DEVELOPMENT AND EVALUATION OF AN ORAL PUSH-PULL OSMOTIC PUMP TABLET OF LOSARTAN POTASSIUM

Dissertation Submitted to

THE TAMILNADU Dr. M.G.R MEDICAL UNIVERSITY

In partial fulfillment for the award of the degree of

MASTER OF PHARMACY
In
PHARMACEUTICS
By

Reg. No: 26101006

Under the Guidance of

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Approved by Pharmacy Council of India, New Delhi, and
All India Council for Technical Education. New Delhi.

THE CERTIFICATE

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DECLARATION

I do hereby declare that the thesis entitled **"DEVELOPMENT AND FORMULATION OF AN ORAL PUSH-PULL OSMOTIC PUMP TABLET OF LOSARTAN POTASSIUM"** by **Reg. No: 26101006** submitted in partial fulfillment for degree of **Master of Pharmacy in Pharmaceutics** was carried out at C. L. Baid Metha college of Pharmacy, Chennai-97 under the guidance and supervision of **DR. R. KUMARAVELRAJAN M. Pharm., Ph.D.,** during the academic year 2011-2012. The work embodied in this thesis is original, and is not submitted in part or full for any other degree of this or any other University.

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List of Abbreviations

COPD	-	Chronic Obstructive Pulmonary Disease
PPOP	-	Push- pull Osmotic Pump
KCl	-	Potassium Chloride
Nacl	-	Sodium Chloride
HCl	-	Hydrogen chloride
API	-	Active Pharmaceutical Ingredient.
GI	-	Gastro Intestine
ACE	-	Acetylcholine esterase
I.P	-	Indian Pharmacopeia
USP	-	United States Pharmacopeia
IVIVC	-	*Invitro Invivo* Correlation
Std.	-	Standard
Sam.	-	Sample
Fig.	-	Figure
NMT	-	Not more than
NLT	-	Not less than
Avg. wt.	-	Average weight
RT	-	Room temperature
SD	-	Standard deviation
UV	-	Ultraviolet
MPDRS	-	Multiple particulate Delayed Release System
L-OROS	-	Liquid Oral Osmotic System
ODDS	-	Osmotic Drug Delivery System

Nomenclature

atm	-	atmospheric pressure
mg	-	milligram
µm	-	micrometer
w/ w	-	weight / weight
ml	-	millilitres
min.	-	minutes
mm	-	millimetre
%	-	percentage
nm	-	nanometer
h	-	hour
g/ cm^3	-	gram per cubic centimetre

In the recent years, considerable attention has been made in the development of novel drug delivery systems (NDDS) [1]. Among the novel drug delivery systems, per oral controlled drug delivery system plays a vital role in the major market share due to their ease of administration and their capability to improve patient compliance[2]. The *per oral* controlled drug delivery system provides significant benefits over immediate release formulations, moreover these products show reduced side effects due to their simplified dosing schedule. Orally controlled drug delivery system provides greater effectiveness in the treatments of chronic diseased conditions like Chronic obstructive pulmonary diseases(COPD), Cardiac diseases, Diabetes, etc., There are different types of dosage designs are available to modulate or control the drug release from a system. Most of the oral controlled dosage forms include matrix, reservoir or osmotic systems. The matrix systems are made up of either swellable or non-swellable polymers are blended with the active ingredient forms a viscous gel when water has been absorbed by the system and slowly erodes exposing the drug into the surrounding medium. While in the reservoir systems the drug is encapsulated within a water insoluble polymer which allows the drug to diffuse through the membrane into the release medium. The matrix or reservoir type can contain the immediate release dosage form of the drug. However, the release of drug from these systems may be affected by the factors like pH, presence or absence of food and other physiological factors from both conventional and controlled release systems[3]. To eradicate these issues a novel osmotic systems are developed.

Oral osmotically controlled system mainly works on the principle of osmosis. This system utilizes osmotic pressure for the release of drug. Drug release from these systems is independent of pH and other physiological parameter to a large extent and it is possible to modulate the release characteristic by optimizing the properties of drug and system[4]. Various types of oral osmotic pumps are available to control the drug delivery over a prolonged period.

1.1 Principle of Osmosis

Osmosis refers to the movement of solvent from region of lower concentration to a region of higher concentration through semi permeable

membrane. The first osmotic effect was reported by Abbe Nollet in 1748. But the quantitative measurement of osmotic pressure was shown by Peffer in 1877, by performing an experiment in which he attempted to separate sugar solution from pure water through semi-permeable membrane. He also proved that the osmotic pressure of the sugar solution is directly proportional to the concentration of solution and absolute temperature.

Later, Vant Hoff in 1886 identified an existing proportionality between osmotic pressure, concentration of solution and temperature. Based on this he proved proportionality between these results and ideal gas law equation (1) by the following expression

$$\pi = \emptyset cRT \tag{1}$$

where Ø is the osmotic coefficient of the solution (equal to 1 for dilute solutions) and where c is the molar concentration of sugar (or other solute) in the solution, R is the gas constant, and T the absolute temperature. Osmotic pressures for concentrated solution of the solutes are extremely high ranging up to 500 atm. The osmotic pressure can cause high water permeability across the membrane. The water permeability through the membrane by osmosis can be given by the equation (2)

$$\frac{dV}{dt} = \frac{A\theta\Delta\pi}{l} \tag{2}$$

wheredV/dt is the water flow across the membrane of the area$A$, thickness$l$, and osmotic permeability θ in $cm^3.cm/cm^2.h.atm$ and $\Delta\pi$ is the osmotic pressure difference between the two solutions on either side of the membrane. Cellulosic polymers, particularly cellulose acetate are commonly used. Typical values for the osmotic water permeability of cellulosic membranes range from 1 $X10^{-5}$ to 1 $X10^{-7}$ $cm^3.cm/cm^2.h.atm^5$.

1.2 Classification of osmotic controlled drug delivery system

The osmotic pump can be classified into two categories viz., oral osmotic pump and implantable osmotic devices.

1.2.1 Implantable Devices

A. The Rose and Nelson Pump

Rose and Nelson the two Australian physiologists were the first to develop osmotic systems based on the principle of Osmosis[6]. This system comprises of three chambers: a drug chamber, a salt chamber and a water chamber as shown in the **Fig.1**. The drug and water chamber was separated by a rigid semi permeable membrane. The difference in osmotic pressure across the membrane moves water chamber into salt chamber resulting increase in the volume of salt chamber which in turn pumps the drug out of the device[7].

The pumping rate of Rose-Nelson pump is given by equation (3)

$$\frac{dm}{dt} = \frac{dv}{dt} xC \tag{3}$$

wheredMt/dt is the drug release rate, dV/dt is the volume flow of water into the salt chamber, and c is the concentration of drug in the drug chamber.

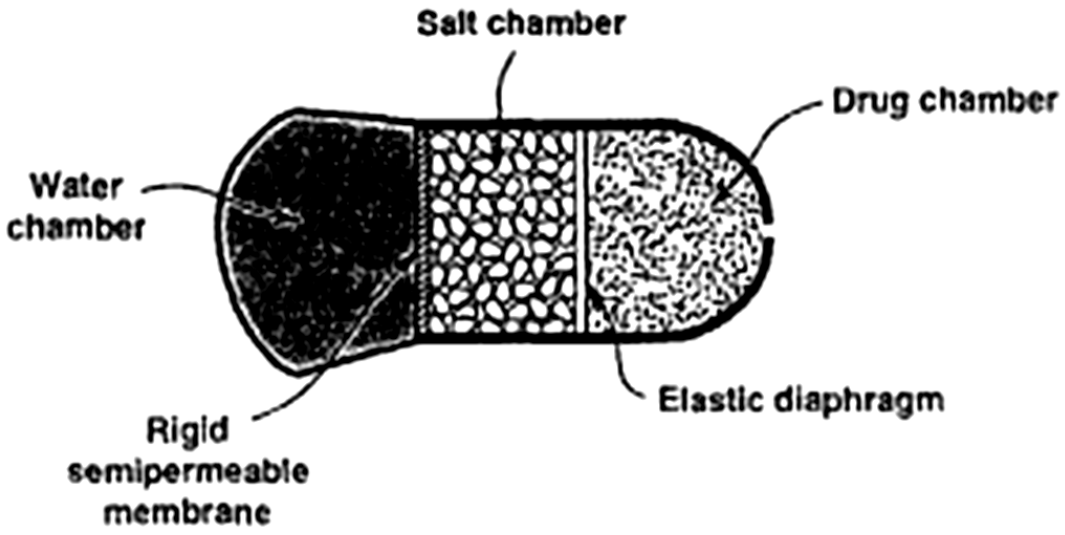

Fig.1 Three chambered Rose-Nelson Osmotic pump

B. Higuchi-Leeper Pump

A number of simplifications of Rose-Nelson pump have been made by Higuchi and Leeper. Higuchi and Leeper simplified Rose-Nelson pump by removing the water chamber from Rose-Nelson device. The Higuchi and Leeper device is activated after the penetration of water inside the device from the surrounding environment. Higuchi Leeper pump is widely used for vertinary use. This type of pump is either implanted or swallowed by the animal for delivery antibiotic or growth hormones. Higuchi Leeper pump consist of rigid semi permeable membrane and an elastic diaphragm made up of microcrystalline paraffin wax (Low melting wax) to separate the drug and osmotic chamber is represented in the **Fig.2**. The pulsatile release was achieved by the production of a critical pressure at which the delivery orifice opens and releases the drug[8].

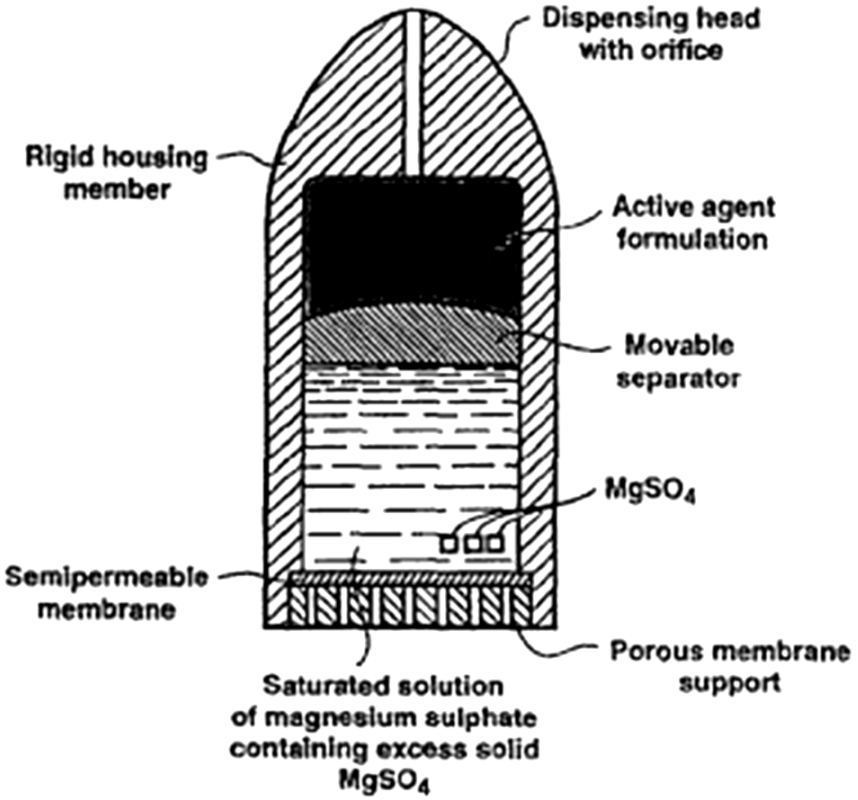

Fig.2 Higuchi-Leeper pump

C. Higuchi Theeuwes Pump

Higuchi and Theeuwes developed variant type of Rose and Nelson pump which is simpler than the Higuchi Leeper pump. The design of Higuchi Theeuwes pump is depicted in **Fig. 3**. This device was made of rigid housing which is made up of semi permeable membrane which is strong enough to withstand the pressure created by the permeation of water. The drug is loaded prior to the application of device. The release of drug from device can be controlled by the salt chamber, permeation capability of the outer membrane and orifice. Mixture of citric acid and sodium bicarbonate in salt chamber in the presence of water generate carbon di-oxide gas, which exert a pressure on the elastic diaphragm, eventually delivers the drug through orifice[9].

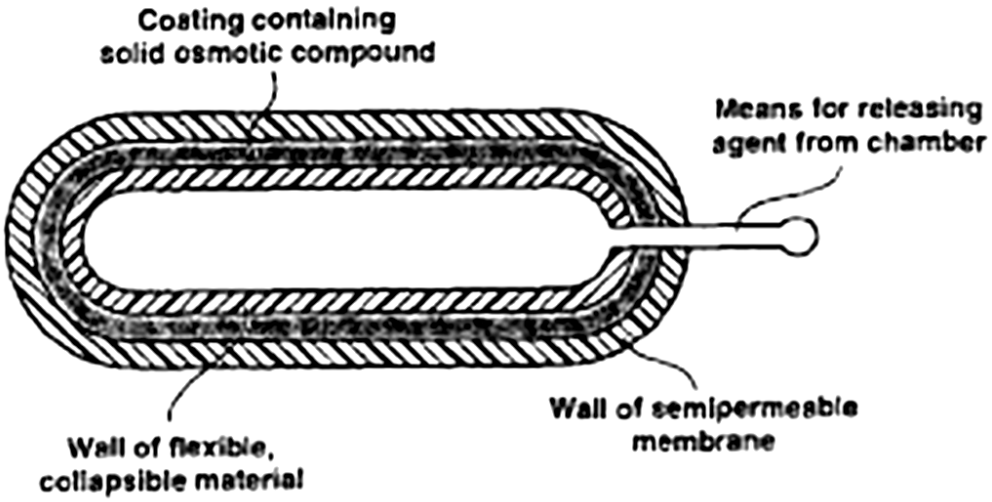

Fig.3 Higuchi Theeuwes Pump

1.2.2 Oral Osmotic Pumps: [10, 11]

The oral osmotic pump can be classified in to following types:

1. **Single Chamber Osmotic Pump**
    - Elementary osmotic pump
2. **Multi Chamber Osmotic Pump**

- Push pull osmotic pump.
- Osmotic pump with non-expanding second chamber.

3. Specific Types

- Controlled porosity osmotic pump.
- Monolithic osmotic systems.
- Bursting osmotic pump.
- Multi particulate delayed release systems.
- Liquid oral osmotic system.

1. Single Chamber Osmotic Pump

Elementary Osmotic pump (EOP):

The elementary osmotic pump (EOP) was introduced by F.Theeuwes shown in **Fig.4**. The EOP consists of an osmotic core, with the drug surrounded by the semi permeable with a delivery orifice. EOP was the simplest form of oral osmotic pumps which are desired to deliver the drug through an aperture at zero order rates.

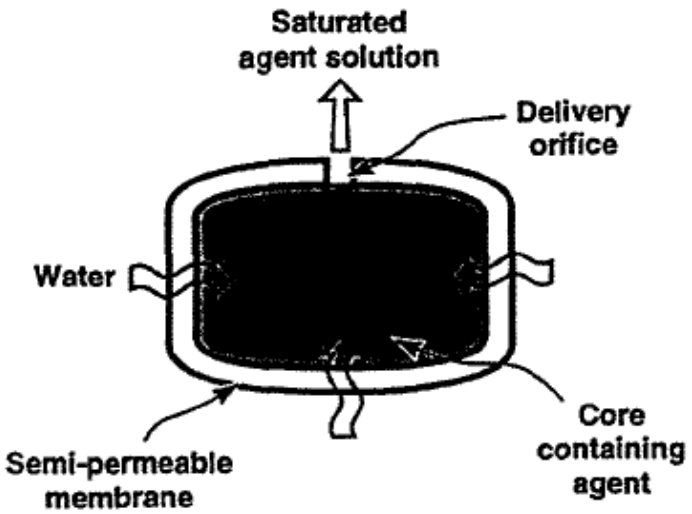

Fig.4 Theeuwes Elementary osmotic pump.

EOP consists of a drug core with an osmogent surrounded by a semi permeable membrane with a delivery orifice. But these elementary osmotic pumps are suitable for the moderately soluble drugs. Most of the drugs are differ in their solubility properties, this parameter can also influence on the selection design which is suitable for the release rate of the drug.

2. Multi Chamber Osmotic Pump

Push-pull osmotic pump (PPOP)

Push-pull osmotic pump is the modification of simple EOP, through which it can deliver both poorly water soluble and freely water soluble drugs at a constant rate[12]. It is a bilayer tablet coated with semi permeable membrane. The PPOP consist of two layers separated usually by an elastic diaphragm. The upper layer contains the drug and it is communicated with the outer environment via a small delivery orifice. A swellable polymer osmotic agent is present in the lower layer comprising of about 20-40 percent of the core tablet weight. The upper drug layer comprises of about 60-80 percent of the tablet weight. PPOP can also be used to deliver drugs which are extremely soluble in water. There are number of modifications are available for altering the release of drug such as delayed push-pull, multilayer push-pull system and Push stick system[13]. **Fig. 5** shows the schematic representation of the push pull osmotic pump before and after operation.

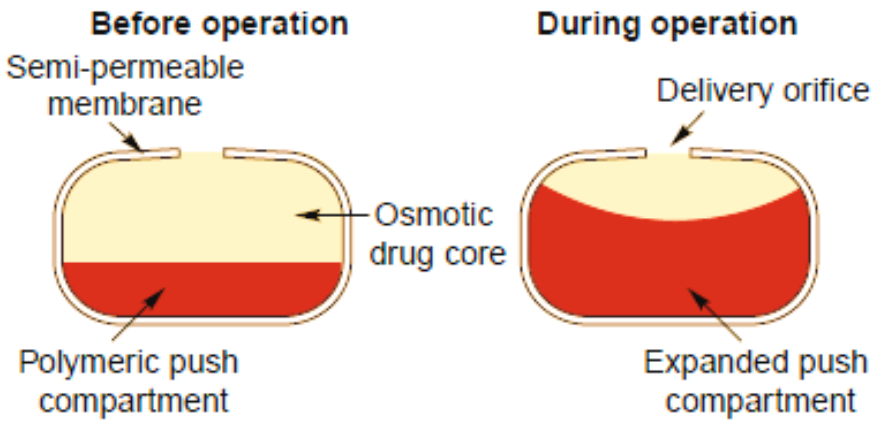

Fig. 5 Push pull osmotic pump

Osmotic pump with non-expanding second chamber

The second category of multi-chamber devices comprises of system containing a non-expanding second chamber. This can be divided into two types based on the nature of the function of second chamber. In one category of these devices, the second chamber is used to produce the drug solution leaving the devices. This can reduce the GI irritation caused due to the saturated solution of the drug that leaves the oral osmotic devices. This type consists of two rigid chamber, the first containing the biologically inert osmotic agent, such as sodium chloride, the second chamber contains the drug. The solution of osmotic agent formed in the first chamber then passes through the connecting hole to the drug chamber where it mixes with the drug solution before exiting through the micro porous membrane that form a part of wall in the surrounding the chamber. The device could be used to deliver relatively insoluble drugs[14].

1.2.3 Specific Types

- **Controlled porosity osmotic pump**

Controlled porosity osmotic pump is a simple form of osmotic pump which consists of drug core surrounded by a semi permeable membrane with water soluble components. These water soluble compounds when comes into contact with water it gets dissolved and forms minute pores through which the active drug molecule is released for desired period of time. In this type the release rate is depends upon water permeability[15], osmotic pressure of the core tablet, thickness of the membrane and total surface area of coating. The water flow rate into the system can be described by equation (4),

$$\frac{dv}{dt} = \frac{Ak}{h} (Dp\text{-}DR) \qquad (4)$$

where k = membrane permeability,
A = Area of the membrane,
Dp = Osmotic pressure difference
DR = Hydrostatic pressure difference

- **Monolithic Osmotic Pump**

Monolithic osmotic pump is comprises of simple dispersion of water soluble agents in a polymer matrix. When the system comes into contact with the aqueous environment, the water imbibition takes place by the active agents and causes the polymer matrix to get rupture resulting in liberation of drug into the outside environment. Initially the rupture starts in the outer polymer matrix and slowly protrudes to the interior polymer matrix in a series. However, this system fails if more than 20 to 30% volume of active agent is incorporated into the device, as above this level, significant contribution from the simple leaching of the substance takes place[16].

- **Bursting Osmotic Pump**

In this type of osmotic pump the drug release is expected to be as same in the EOP. The only difference is the delivery orifice size or absence of the delivery orifice. When it is placed in an aqueous medium the water imbibed and the hydrostatic pressure is built up inside until the wall rupture and the contents are released to the environment. The release rate can be controlled by varying the thickness of the membrane and the area of the membrane. This system is suitable for pulsated release drug delivery mechanism[17].

- **Sandwiched Osmotic Tablets**

It is composed of polymeric push layer sandwiched between two drug layers with two delivery orifices[18]. When placed in the aqueous medium the middle layer containing the swelling agents, swells and pushes the drug through the delivery orifices. The advantage of this type of system is that the drug is released from the two orifices situated in opposite sides of the tablets and thus helps this system to deliver drugs of different solubility simultaneously.

- **Multi Particulate Delayed Release System (MPDRS)**

MPDRS consist of pellets comprises of drug with or without osmotic agent, which are coated with a semi permeable membrane .When this system comes in contact with the aqueous environment, water penetrates in the core and forms a saturated solution of soluble component. The osmotic pressure difference results in rapid expansion of the membrane, leading to the formation of pores. The osmotic agent and the drug released through the pores according to zero order kinetics. The lag time and dissolution rate were found to be dependent on the coating level and the osmotic properties of the dissolution medium[19].

- **Liquid Oral Osmotic System (L-OROS) [20, 21]**

To overcome the drug solubility issue Alza developed the L-OROS system where the liquid soft gelatin product containing the drug in a dissolved state is initially manufactured and then coated with a barrier membrane, then the osmotic push layer and then semi permeable membrane containing a drilled orifice. Liquid OROS are designed to deliver drugs as liquid formulations and combine the benefits of extended release with high bioavailability.

They are of two types: -

- L- OROS Hard cap,
- L- OROS Soft cap

Each of these systems includes a liquid drug layer, an osmotic engine or push layer and a semi permeable membrane coating. When the system is in contact with the aqueous environment water permeates across the rate controlling membrane and activate the osmotic layer. The expansion of the osmotic layer results in the development of hydrostatic pressure inside the system, thereby forcing the liquid formulation to be delivered from the delivery orifice. Whereas L OROS hardcap or softcap systems are designed to provide continuous drug delivery, the L OROS delayed liquid bolus drug delivery system is designed to deliver a pulse of liquid drug. The delayed liquid bolus delivery system comprises three layers: a placebo

delay layer, a liquid drug layer and an osmotic engine, all surrounded by rate controlling semi permeable membrane. The delivery orifice is drilled on the placebo layer end of the capsule shaped device. When the osmotic engine is expands, the placebo is released first, delaying release of the drug layer. Drug release can be delayed from I to 10 hour, depending on the permeability of the rate controlling membrane and thickness of the placebo layer.

1.3 Basic Elements of Oral Osmotic Controlled Drug Delivery Systems[22]

An osmotic pump should contain the following components to attain the desired control over the drug release.

- Drug
- Osmotic agent
- Polymer
- Delivery orifice
- Semi permeable membrane

Drug

The drug candidate should possess the following characteristics to be designed as an oral osmotic drug delivery system.

- ✓ Short biological half-life (2-6 hours)
- ✓ The drug must be highly potent
- ✓ Used to treat chronic diseases like Cardiac diseases, asthma, diabetes, etc.,
- ✓ Drugs like Nifedipine, Salbutamol, Theophylline, Glipizide etc., are suitable candidates for oral osmotic drug delivery system.

Osmotic Agent

Osmogents used for the design of osmotic dispensing device areinorganic or organic in nature a water soluble drug can itself serve as an osmogent.

Inorganic Osmogents

Magnesium sulphate, Sodium chloride, Sodium sulphate, Potassiumchloride, Sodiumbicarbonate.

Polymer

Mostly hydrophilic polymers are preferred in Oral osmotic drug delivery system to provide controlled release of the drug. Sodium carboxymethyl cellulose, Hydroxypropyl Methylcellulose, HydroxyEthylcellulose, Methyl cellulose, PolyEthyleneoxide, Polyvinyl Pyrollidone.

Delivery Orifice

Delivery orifice plays a vital role in controlling the release rate of drug from the osmotic system. The size of the orifice does not show any significant variation in drug release if it is altered within certain limits.

Semipermeable Membrane

The semi permeable membrane must be stable to both the inner and outer environment of the delivery system. The membrane must be rigid enough to withstand the pressure produced by the osmotic agent when it is exposed to the release media. The membrane should be highly permeable to water and impermeable to the drug contents and the dispenser so that the osmogent is not lost by diffusion across the membrane. Moreover the membrane should abide with the biological system.

1.4 Advantages and Disadvantagesof Oral Osmotic Controlled Drug DeliverySystems [23, 24, 25]

Osmotic drug delivery system for oral and parenteral use offer distinct and practical advantage over other means of delivery. The advantages of the osmotic controlled drug delivery systems are as follows:

- It provides a zero order release of drug after an initial lag period.
- The release of drug can be modulated or delayed if desired.
- Drug release from this system is independent of pH and other physiological factors.
- Release rate from this system is highly predictable and minimally affected by the presence or absence of food, which can be easily programmed by altering the release control parameters.
- *In-vitro in-vivo* correlation (IVIVC) obtained from this osmotic pump is highly reliable.
- Drugs of different solubility can be fabricated by this technique.
- Delivery rate of the drug from this system is independent of agitation, delivery orifice provided some limitations.
- An osmotic delivery system is capable of providing not only a prolonged zero-order release, but also a delivery rate much higher than that achievable by the solution-diffusion mechanism.

1.4.1 Disadvantages of Oral Osmotic Controlled Drug Delivery Systems

- Expensive.
- Termination of therapy is not possible in case of any unexpected adverse effects.
- Rapid development of Tolerance.

1.5 Drug release rate controlling factors [26, 27]

There are three significant parameters which can be altered to modulate the release rate of the drug from the oral osmotic controlled drug delivery system.

- ✓ Solubility
- ✓ Osmotic pressure
- ✓ Size of the delivery orifice
- ✓ Membrane thickness

1.5.1 Solubility

The solubility of the Active Pharmaceutical Ingredients (API) should be in the desired range such that the release rate can be optimized based on the solubility property of the drug. In case of poorly soluble drugs the solubility can be modulated within the core tablet by using suitable agents to enhance solubility and to produce the effective release pattern of the drugs.

Solubility Enhancement Methods

- Use of cyclodextrin derivatives are known to improve the solubility of the poorly soluble drugs.
- Change in the nature of the salt form can be able to change the solubility of the drug.
- Solubility modifier excipients are used in the form mini-tablet coated with rate controlling membrane.
- Different types of excipients are available for modulation of pH dependent solubility of APIs.

1.5.2 Osmotic Pressure

The next release controlling factor is the osmotic pressure gradient between inside the compartment and the external environment. The osmotic pressure

difference across the membrane controls the release rate of the drug from the system. The simplest way to achieve a constant osmotic pressure within the compartment is to maintain an osmotic agent with in the compartment. **Table 1** shows the osmotic pressure produced by the solutes used in the controlled release formulations.

1.5.3 Size of the Delivery Orifice

To attain a desired zero order release the size of the delivery orifice should be minimum than the maximum size of the delivery orifice. Usually the delivery orifice size ranges from 300μm to 1mm.

Table 1List of osmotic agents commonly used in osmotic systems[28]

S. No.	Compounds of mixture	Osmotic pressure (atm)
1.	Lactose-Fructose	500
2.	Dextrose-Fructose	450
3.	Sucrose-Fructose	430
4.	Mannitol-Fructose	415
5.	Sodium chloride	356
6.	Fructose	335
7.	Lactose-Sucrose	250
8.	Potassium chloride	245
9.	Lactose-Dextrose	225
11.	Dextrose-Sucrose	190
13.	Sucrose	150
15.	Dextrose	82
17.	Mannitol	38
18.	Lactose	23

Table 2 Patents of drug formulation in the form of elementary osmotic pump[28]

Year	U.S. Patent No.	Drug
1986	4612008	Diclofenac sodium
1988	4765989	Nifedipine and α blocker
1988	4783337	Calcium antagonist, ACE inhibitor
1989	4812263	Isadipine
1989	4837111	Doxazocin
1989	4859470	Diltiazem
1990	4904474	Beclomethasone
1990	4948593	Contraceptive Steroid
1991	5024843	Glipizide
1991	5028434	Nivadipine
1992	5160744	Verapamil
1992	5091190	Glipizide
1993	5185158	Tandopirone
1993	5192550	Antiparkinsons drug
1993	5248310	Beclomethasone (oral)
1996	5545413	Glipizide
1997	5591454	Glipizide
2003	20030224051	Oxycodone
2004	20040091529	Topiramine
2005	20050232995	Resperidone and Paliperidone

Table 3Patents of drug formulations in the form of multi chamber osmotic pump[28]

Year	U.S. Patent No.	Drug
1981	4265874	Indomethacin
1981	4305927	Acetazolamide
1984	4439195	Theophylline
1984	4484921	Theophylline
1986	4610686	Haloperidol
1987	4662880	Pseudoephedrine &Bromopheniramine
1988	4732195	Haloperidol
1988	4751071	Salbutamol
1989	48573300	Chlopheniramine
1991	4986987	Imenhydrinate
1992	147654	Buccal nicotine
1993	200194	Mucosal delivery of anti-plague agent and nicotine
1998	5776493	Mucosal delivery of Nystatin
1999	5869096	Mucosal osmotic delivery of Levodopa
2003	20030143272	Nifedipine formulation
2005	20050053653	Low water soluble drugs

List of Marketed Products Available

Acutrim

- ActivePharmaceutical Ingredient: Phenylpropanolamine Hcl
- Design : Elementaryosmotic pump
- Dose : 75 mg

Alpress LP

- Active Pharmaceutical Ingredient : Prazosin
- Design : Push-Pullosmotic pump
- Dose : 2.5,5 mg

CarduraXL

- Active Pharmaceutical Ingredient : Doxazosin
- Design : Push-Pullosmotic pump
- Dose : 4,8 mg

CoveraHS

- Active Pharmaceutical Ingredient :Verapamil
- Design :Push -Pullosmoticpump with time delay
- Dose : 180, 240 mg

DitropanXL

- Active Pharmaceutical Ingredient :Oxybutinin chloride
- Design :Push–Pullosmoticpump
- Dose : 5, 10 mg

DynacircCR

- Active Pharmaceutical Ingredient :Isradipine
- Design :Push–Pullosmoticpump
- Dose : 5, 10 mg

Efidac 24

- Active Pharmaceutical Ingredient :Pseudoephiderine
- Design :ElementaryPump
- Dose : 60 mg IR, 180 mg CR

Efidac 24

- ActivePharmaceuticalIngredient:Chlorpheniraminemeleate
- Design :ElementaryPump
- Dose : 4 mg IR, 12mgCR

GlucotrolXL

- Active Pharmaceutical Ingredient :Glipizide
- Design :Push-Pullosmotic pump
- Dose : 5, 10 mg

Sudafed 24®

- Active Pharmaceutical Ingredient :Pseudoephedrine Hcl
- Design :Elementary osmotic pump

Volmex®

- Active Pharmaceutical Ingredient :Albuterol
- Design :Elementary osmotic pump

Minipress XL®

- Active Pharmaceutical Ingredient :Prazocine
- Design :Elementary osmotic pump

Procadia XL®

- Active Pharmaceutical Ingredient :Nifedipine
- Design : Push-Pullosmotic pump

Invega®

- Active Pharmaceutical Ingredient :Paliperidone
- Design : Push-Pull osmotic pump

Viadur®

- Active Pharmaceutical Ingredient :Leuprolide acetate
- Design **:**Implantable osmoticsystem

ChronogesicTM

- Active Pharmaceutical Ingredient : Sufentanil
- Design :Implantable osmoticsystem

1.6 Hypertension and Management[29]

High blood pressure (HBP) or hypertension means high pressure (tension) in the arteries. Arteries are vessels that carry blood from the pumping heart to all the tissues and organs of the body. High blood pressure does not mean excessive

emotional tension, although emotional tension and stress can temporarily increase blood pressure. Normal blood pressure is below 120/80; blood pressure between 120/80 and 139/89 is called "pre-hypertension", and a blood pressure of 140/90 or above is considered high. The systolic blood pressure corresponds to the pressure in the arteries as the heart contracts and pumps blood forward into the arteries. The bottom number, the diastolic pressure, represents the pressure in the arteries as the heart relaxes after the contraction. The diastolic pressure reflects the lowest pressure to which the arteries are exposed.The pressure exerted by blood within the artery is shown in**Fig. 6**.

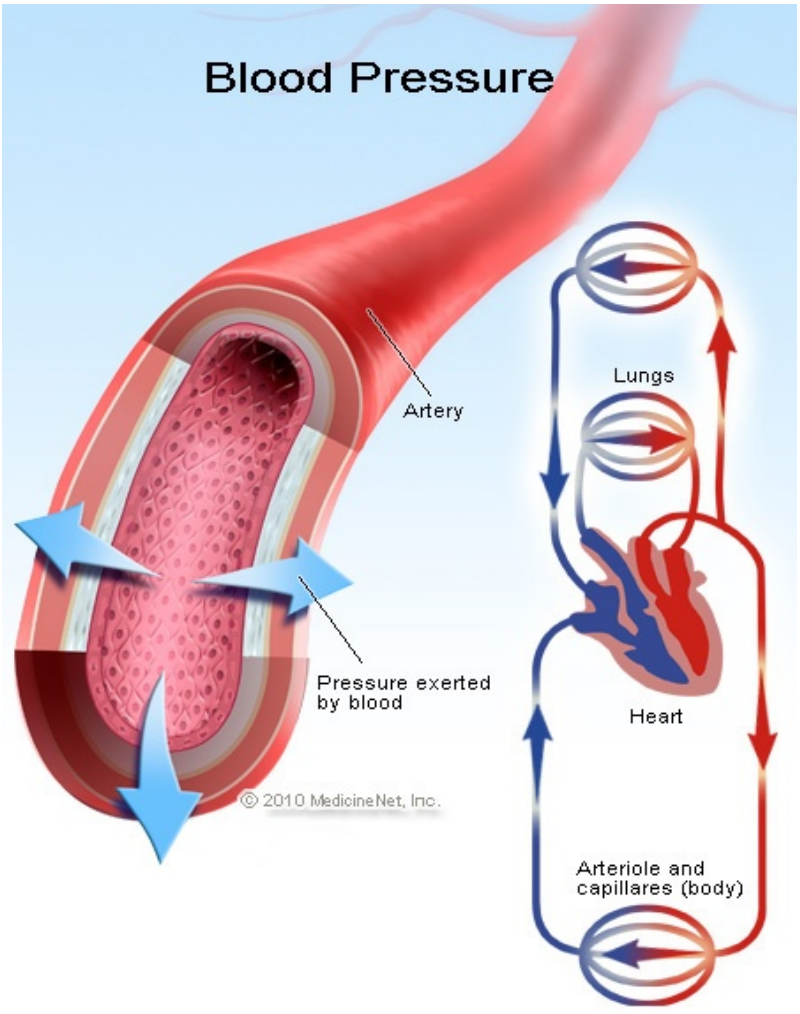

Fig. 6Blood pressure within the artery

An elevation of the systolic or diastolic blood pressure increases the risk of developing cardiac disease, renal disease, atherosclerosis or arteriosclerosis, eye damage, and stroke. These complications of hypertension are often referred to as end-organ damage because damage to these organs is the end result of chronic high blood pressure. For that reason, the diagnosis of high blood pressure is important so efforts can be made to normalize blood pressure and prevent complications. It was previously thought that rises in diastolic blood pressure were a more important risk factor than systolic elevations, but it is now known that in people 50 years or older systolic hypertension represents a greater risk. Hypertension is clearly a major public health problem.

1.7.1 Management of Hypertension:

- Diuretics
  - Thiazides: Hydrochlorothiazide, Chlorthalidone, Indapamide
  - High ceiling: Furosemide, etc.
  - K' Sparing: Spironolactone,Amiloride
- ACE inhibitors
  - Captopril, Enalapril, Lisinopril, Perindopril, Ramipril, Fosinopril, etc.
- Angiotensin (AT, receptor) blockers
  - Losartan, Candesartan, Irbesartan, Valsartan, Telmisartan
- Calcium channel blockers
  - Verapamil, Diltiazem, Nifedipine, Felodipine, Amlodipine, Nitrendipine, Lacidipine, etc.
- Adrenergic blockers
  - Propranolol, Metoprolol, Atenolol, etc.
- B Adrenergic blockers
  - Labetalol, Carvedilol
- α Adrenergic blockers
  - Prazosin, Terazosin, Doxazosin, Phentolamine, Phenoxybenzamine
- Centralsympatholytics
  - Clonidine, Methyldopa
- Vasodilators
  - Arteriolar: Hydralazine,Minoxidil,Diazoxide
  - Arteriolar + uenlus: Sodium nitroprusside

2. Review of Literature

- **Zhi-hong Zhang *et al.*,**[30] have designed an expert system for the selection of excipients and the method for the preparation of push pull osmotic pump containing poorly water soluble drugs. For this work they had chosen Famotidine as a model drug. Neural networks, VB.NET associating with SQL server were used to design the expert system. Till now this is the only expert system available for designing of controlled drug delivery systems.

- **Chanmanlal Shishoo *et al.*,**[31] the push-pull osmotic pump have been developed for zero order delivery of Lithium Carbonate for a period of 24 h. The effect of various formulation variables on bilayer core tablet and its semi permeable coating along with orifice diameter have been investigated and optimized for desired drug release profile. Drug release was found to be inversely proportional to the membrane thickness but directly related to the amount of pore formers in the semipermeable membrane. Images from a scanning electron microscope confirmed the presence of pores in the semipermeable membrane which facilitated the required water penetration. No distortion or change in orifice shape was noticed prior to and after the dissolution study. Drug release from the developed formulation was found to be independent of pH, agitation intensity and agitation mode but depended on osmotic pressure of dissolution media.

- **Rajagopal Kumaravelrajan *et al.*,**[32] Controlled porosity osmotic pump tablet(CPOP) system was designed to deliver Nifedipine (NP) and Metoprolol (MP) in a controlled manner up to 12 h. Formulation variables like type and level of pore former and percent weight gain of membrane was found to affect the drug release from the developed formulations. Drug release was inversely proportional to the membrane weight but directly related to the level of pore former. Burst strength of the exhausted shell was inversely proportional to the level of pore former, but directly affected by the

membrane weight. Results of scanning electron microscopy (SEM) studies showed the formation of pores in the membrane from where the drug release occurred. Dissolution models were applied to drug release data in order to establish the mechanism of drug release kinetics. In vitro release kinetics was subjected to superposition method to predict *in vivo* performance of the developed formulation. The developed osmotic system is effective in the multi-drug therapy of hypertension by delivering both drugs in a controlled manner.

- **K Latha *et al.*,**[33]developed an optimized press-coated tablet of Losartan Potassium using a mixture of hydrophilic polymer, Hydroxy propyl methylcellulose (HPMC) and microcrystalline cellulose (MCC) in order to achieve a predetermined lag time for chronotherapy. The press-coated tablets (PCT) containing Losartan Potassium in the inner core were prepared by compression-coating with HPMC 100KM alone and admixed with MCC as the outer layer in different ratios. The optimised formulation was further characterized with Fourier-transform infrared spectroscopy (FTIR) and powder X-ray diffractometry (PXRD) to investigate any drug/excipient modifications/interactions. The release profile of the press-coated tablet exhibited a distinct lag time before burst release of Losartan Potassium. Lag time was dependent on the ratio of HPMC/MCC in the outer shell. The lag time was from 0.5 to 18.5 h and could be modulated as it decreased as the amount of MCC in the outer layer increased. There was no modification or chemical interaction between the drug and the excipient. Formulation LPP2, with HPMC/MCC of (30:70) in the outer shell and showing a predetermined lag time of 6 h prior to burst release of the drug from the press-coated tablet was taken as the optimized formulation.

- **Stuti Gupta *et al.*,**[34] Studied Conventional drug delivery systems of have little control over their drug release and almost no control over the effective concentration at the target site. This leads to constantly changing, unpredictable plasma concentrations. Drugs can be delivered in a controlled pattern over a long period of time by the process of osmosis. Osmotic

devices are the most promising strategy based systems for controlled drug delivery. They are the most reliable controlled drug delivery systems and could be employed as oral drug delivery systems. The present review is concerned with the study of drug release systems which are tablets coated with walls of controlled porosity. When these systems are exposed to water, low levels of water soluble additive is leached from polymeric material i.e. semi permeable membrane and drug releases in a controlled manner over an extended period of time. Drug delivery from this system is not influenced by the different physiological factors within the gut lumen and the release characteristics can be predicted easily from the known properties of the drug and the dosage form. In this paper, various types of osmotically controlled drug delivery systems and the basic components of controlled porosity osmotic pump tablets have been discussed briefly.

- **Tanmoy Ghosh *et al.*,**[35] Formulated Immediate release conventional dosage form lack in the efficiency of controlling the proper plasma drug concentration. This results in the development of various controlled drug delivery system. Among which the Pulsatile drug delivery systems (PDDS)/ osmotic drug delivery system (ODDS) are gaining importance as these systems deliver the drug at specific time as per the path physiological need of the disease, resulting in improved patient therapeutic efficacy and compliance. They work on the principle of osmotic pressure for controlling the delivery of the drug. The release of the drug is independent of physiological factors of the Gastro Intestinal Tract GIT to a large extent. This review highlights' the theoretical concept of drug delivery, history, types of oral osmotic drug delivery systems, factors affecting the drug delivery system, advantages and disadvantages of this delivery systems ,theoretical aspects, applications, marketed status and last but not the least the recent development.

- **Kh.Hussan Reza *et al.*,**[36] developed a monolithic osmotic tablet of Aceclofenac coated with cellulose acetate (CA) and membrane drilled with two orifices on both side surfaces, has been described. The influences of

tablet formulation variables including amount of polymer Explotab (Expt), amount of sodium chloride (NaCl), have been investigated. Orifice size and membrane variables including nature and amount of plasticizers as well as thickness on drug release have also been studied. The in vitro release profiles of the optimal system have been evaluated in various release media and different agitation rates, and compared with commercialized conventional tablet. It was found that the amount of Explotab and Nacl showed profoundly positive effects on drug release. It could be found that the optimal orifice size was 800 μm. It has also been observed that hydrophilic plasticizer polyethylene glycol (PEG) improved drug release, when they were incorporated in CA membrane. The monolithic osmotic tablet system was found to be able to deliver Aceclofenac at the rate of approximate zero-order up to 24 h, independent of both environmental media and agitation rate. The monolithic osmotic tablet system may be used in drug controlled delivery field, especially suitable for water-insoluble drugs.

- **R.Vijaya Muthumanikandar *et al.*,**[37] The buccoadhesive controlled release tablets of Losartan Potassium were prepared by Wet granulation method using the Carbopol 934P, HydroxyPropylcellulose, sodium alginate and sodium CMC as bioadhesive polymer. The tablets were evaluated for the Pre-compression Parameters and post compression parameter like bioadhesive strength, *In vitro* retention time, and *In vitro* drug release study. The thickness and weight of the tablets, respectively, ranges from 2.3 ± 0.01 and 2.5 ± 0.02 and the weight of tablets ranges from 148-152mg.The Formulation containing sodium CMC and Sodium alginate shows acceptable bioadhesive strength but erode respectively, with in 6 to 8 hours. The tablet formulation containing carbopol and HPC shows higher bioadhesive strength, sustained release of drug and sufficient *In vitro* retention time. The optimized formulation obeys the first order release kinetics.

- **Beom-Jin Lee *et al.*,**[38] were prepared solid dispersion granules of a poorly water soluble drug. For this study Losartan potassium was chosen as the model drug because of its pH dependent solubility and short elimination

half- life. A free flowing Solid dispersion granule was prepared by adsorbing the melt of the drug and poloxomer 188 onto the aerosil followed by direct compression with polyethylene oxide to obtain an solid dispersion loaded sustained release matrix tablets. This study concluded that a combination of solid dispersion techniques using surface adsorption and sustained release concepts is a promising approach to control the release rate of a poorly water soluble drug in a pH independent manner.

- **R.Kumaravelrajan *et al.,*[39]** had developed a prototype design for simultaneous drug delivery for multidrug therapy in the treatment of hypertension. The system composed of a middle push layer and attached drug layers of Nifedipine and Metoprolol resembles like a sandwich. In this article Polyethylene oxide of 600,000 and 8,000,000 g/mole were used as thickening agent in the drug layer and as an expandable hydrogel for push layer. Amount of polyethylene oxide and KCl had profound influence on drug release has been observed. Further the release of drugs was optimized by size of the delivery orifice, level of plasticizer and membrane thickness. The optimal osmotic pump was found to deliver both Nifedipne and Metoprolol tatarate simultaneously for extended period of time.

- **Prajapati B.G *et al.,*[40]** developed hydrophilic polymer and hydrophobic polymer based matrix Losartan Potassium sustained release tablet which can release the drug up to time of 24 hrs in predetermined rate. Influence of hydrophilic and hydrophobic polymer on Losartan potassium was studied. Administration of LP in a sustained release dosage would be more desirable for antihypertensive effects by maintaining the plasma concentrations of the drug well above the therapeutic concentration. From in vitro dissolution profile LP prepared with blend of HPMC K4M (67.2 mg), HPMC K200M (90mg) and Eudragit RSPO (112.5 mg), where drug release was about 94-98% and also showed highest similarity factor values.

- **Marina Koland *et al.,*** [41]Mucoadhesivebuccal films of Losartan Potassium were prepared using Hydroxypropyl Methylcellulose and retardant polymers Ethyl cellulose or Eudragit RS 100. The mucoadhesive force, swelling index, tensile strength and percentage elongation at break was higher for those formulations containing higher percentage of HPMC. In vitro drug release studies reveal that all films exhibited sustained release in the range of 90.10 to 97.40 % for a period of 6 hours. The data was subjected to kinetic analysis which indicated non-fickian diffusion for all formulations except E2. *Ex vivo* permeation studies through porcine buccal mucosa indicate that films containing higher percentage of the mucoadhesive polymer HPMC showed slower permeation of the drug for 6-7 hours.

- **Robert Gurny *et al.,*** [42]in this article, the development of oral osmotic pump during the past 30 years had been observed. Interesting fact is that the production of oral osmotic pump has been doubled in the past ten years. In this article they have reviewed the crowded patents and manufacturing technologies, specific products and their clinical use.

- **Vincent Maleterre *et al.,*** [43]had done this investigation to understand which factors have an effect on the drug delivery for modelling the drug release and to develop a mathematical model predictive of the drug release kinetics. For this study they had chosen two model drugs, Isradipine (ISR) and Chlophenaramine which are practically insoluble and freely soluble drugs. Results show that, regardless of the drug properties which do not significantly affect the drug delivery, the release kinetics is mainly controlled by four factors, (i) the PEG proportion in the membrane, (ii) the tablet surface area, (iii) the osmotic agent proportion and (iv) the drug layer polymer grade. A mathematical approach was developed to predict the drug delivery kinetics varying the PPOP controlling factors and helps to more efficiently design PPOP.

- **Karsten Mader *et al.,*** [44] the mechanism of drug release from push-pull osmotic systems has been investigated by Magnetic Resonance Imaging

using a new benchtop apparatus. The results showed that (i) hydration and swelling critically depend on the tablet core composition, (ii) high osmotic pressure developed by the push layer may lead to bypassing the drug layer and incomplete drug release and (iii) the hydration of both the drug and the push layers needs to be properly balanced to efficiently deliver the drug.

- **Vincent Malattere *et al.,*** [45]carried out the study to investigate coating characteristics of push–pull osmotic systems using three-dimensional terahertz pulsed imaging (3D-TPI) and to detect physical alterations potentially impacting the drug release. The terahertz time-domain reflection signal was used to obtain information on both the spatial distribution of the coating thickness and the coating internal physical mapping. The results showed that (i) the thickness distribution of push pull osmotic system coating can be non-destructively analysed using 3D-TPI and (ii) internal physical alterations impacting the drug release kinetics were detectable by using the terahertz time-domain signal. The implementation of terahertz pulsed imaging as quality control analytical tool in the development and the manufacturing may represent a major step forward to improve the design, the scalability and potentially the quality control during the routine manufacture of push–pull osmotic.

- **Longxiao Liu *et al.,*** [46]developed a method for preparation of monolithic osmotic pump tablet by modulating Atenolol solubility with acid. Tartaric had chosen as solubility promoter, sodium chloride as osmotic agent and polyvinyl pyrrollidone as retardant agent. The approach of solubility – modulated by acid alkali reaction might be used for the preparation of osmotic pump tablet for other poorly soluble drugs with alkaline or acid groups. The results showed that the optimal monolithic osmotic pump tablet was able to deliver atenolol at the rate of zero order upto 24 hours and also independent of release media and agitation rate.

- **Wakode R *et al.,*** [47]An oral push-pull system that can deliver Pramipexole developed and compared with other types of osmotic delivery systems, such

as an asymmetric membrane coating and a dense coat with mechanical drilling. An optimized system was selected to study the effect of the concentration of a pore-forming agent such as PEG 400 and dibutyl phthalate, the pH of dissolution media, the effect of agitation and osmotic agents on drug release. The osmotic pressure generated was determined using a 3D3 freezing point osmometer. The drug release was found to follow zero order kinetics. Drug release increased with an increase in osmotic pressure. The developed push-pull osmotic system showed the desired once-a-day release kinetics.

- **Longxiao Liu *et al.*,** [48]proved that a bilayer core osmotic pump does not require laser drilling to form the delivery orifice. Bilayer consists of two layers (a) drug layer and (b) push layer was made with modified upper tablet punch. The indented tablets were coated by conventional pan coating process. For this study they had chosen Nifdipine as a drug model. Sodium chloride as osmotic agent, polyvinylpyrollidine as suspending agent, croscarmellose sodium as expanding agent. Ethyl cellulose with PEG 400 was used as the coating membrane. The optimized formulation showed zero order release for 24 hours, independent of media and agitation. By this effort the preparation of bilayer core osmotic pump have simplified.

- **Shruthi Chopra *et al.*,** [49]The aim of the research work was to systemically device a model of factors that would yield an optimized sustained release dosage form of an anti-hypertensive agent, Losartan Potassium, using response surface methodology by employing a 3-factor, 3-level Box-Behnken statistical design. Independent variables studied were the amount of the release retardant polymers – HPMC K15M (X1), HPMC K100M (X2) and sodium carboxymethyl cellulose (X3). The dependent variables were the burst release in 15 min (Y1), cumulative percentage release of drug after 60 min (Y2) and hardness (Y3) of the tablets with constraints on the Y2 = 31–35%. Statistical validity of the polynomials was established. In vitro release and swelling studies were carried out for the optimized formulation and the data were fitted to kinetic equations. The polynomial mathematical

relationship obtained Y 2 ¼ 32:91 - 2:30X1 - 5:69X2 - 0:97X3 - 0:41X1X2 þ 0:21X1X3 - 0:92X21-1:89X2 2 ðr2 ¼ 0:9944Þ explained the main and quadratic effects, and the interactions of factors influencing the drug release from matrix tablets. The adjusted (0.9842) and predicted values (0.9893) of r2 for Y2 were in close agreement. Validation of the optimization study indicated high degree of prognostic ability of response surface methodology. Tablets showed an initial burst release preceding a more gradual sustained release phase following a non-fickian diffusion process.

- **B. Mishra *et al.,*** [50]was aimed to evaluate and formulate oral osmotic pumps of Pentazocine HCl expected to deliver prolonged period of time with reduced frequency of dosing. Push-pull osmotic pump of Pentazocine HCl were prepared using different formulation variables such as pore diameter of delivery orifice, presence of surfactant, presence of osmopolymer and presence or absence of water soluble polymer. The results showed that the presence of surfactant and osmopolymer in the formulation influences the drug release. All formulations with different formulation variable showed controlled release with initial 2 hour lag phase.

- **Suresh P. Vyas *et al.,*** [51] developed an oral osmotic pump which can able to deliver Theophylline and Salbutamol sulphate in the multidrug therapy of asthma. A modified bi-layered push pull osmotic pump was developed using basic designs of various oral osmotic pumps. This system was developed initially with theophylline and optimized with two different types of theophylline with varying amount of hydrophilic polymer mixture in the upper layer and polyethylene oxide in lower layer which is expandable. Similarly the release of salbutamol sulphate was also optimized. Finally the release rate of both drugs was compared with respective marketed controlled release formulations. The optimized formulation was taken in order to study the effect of different variables.

- **Pradeep R.Vavia *et al.,*** [52] developed a controlled porosity osmotic pump of Pseudoephedrine, with cellulose acetate as semipermeable membrane with

different channelling agents like, diethylphthalate, dibutylphthalate, dibutylsebacate and polyethylene glycol. The drug release is directly proportional to the concentration of the osmotic agent used, to retard the release rate and to provide the desired zero order release by adding suitable channelling agents. In this study, diethylphthalate with plasticizer like PEG 400 showed effective release upto 12 hours. From this article it has been concluded that the desired zero order release profile can be obtained by optimizing the drug:osmogent ratio, polymer concentration and the channelling agent type and concentration.

- **Sanjay Garg *et al.,*** [53] in this article they had reviewed, different types of oral osmotic systems and also various aspects governing drug release from these systems, and critical formulation factors are discussed. Osmotically controlled oral drug delivery systems utilize osmotic pressure for controlled delivery of active agent(s). Drug delivery from these systems, to a large extent, is independent of the physiological factors of the gastrointestinal tract and these systems can be utilized for systemic as well as targeted delivery of drugs. The release of drug(s) from osmotic systems is governed by various formulation factors such as solubility and osmotic pressure of the core component(s), size of the delivery orifice, and nature of the rate-controlling membrane. By optimizing formulation and processing factors, it is possible to develop osmotic systems to deliver drugs of diverse nature at a pre-programmed rate. They have concluded that by modulating the formulation factors it is possible to use this system to deliver drugs of diversified nature.

- **Bertil Abrahamsson *et al.,*** [54] compared the bioavailability of Nifedipine when administered as a hydrophilic matrix tablet (ER) and a push–pull osmotic pump tablet (XL) administrated after fasting, and to evaluate the effect of food for the hydrophilic matrix tablet. For this purpose, three separate studies were performed on healthy volunteers (*n*558) including gammascintigraphic monitoring of tablet erosion and localisation in the gastrointestinal tract for ER in one study. Both ER and XL provided almost constant drug delivery over 24 h, after administration under fasting

conditions, and bioequivalence was obtained according to 90% confidence intervals of the difference between formulations within 80–125% for *C* and max AUC. Food significantly increased AUC for ER but no significant difference was obtained between ER and XL with food with respect to extent of bioavailability. The rate of absorption was increased to a higher degree for ER than for XL, as indicated by a *C* which was almost twice as high for ER compared with XL. The results concluded that effect of food motility on rate of absorption. The extent of Nifedipine bioavailability appeared also influenced by food but a steady state would be needed to ascertain the true magnitude.

- **Giancarlo Santus *et al.*,** [55]reviewed U.S. patents on osmotic drug delivery through December 1993.In this they have reviewed around 240 patents cover a period of a little 20 years. They had mentioned list of patents obtained right from the beginning by Felix Theeuwes. This review helps to guide the patent literature in the field of osmotic devices.

- **Gaylen M. Zenter et *al.*,**[56]developed a controlled porosity osmotic pump of Diltiazem Hydrochloride and modulated its solubility property (reduced) for an extended period of 12-14 h through incorporation of controlled release sodium chloride elements into the core tablet formulations. Other Diltiazem Hydrochloride core tablets were prepared which contained the positively charged anion-exchange resin (poly (4-vinylpyridine). In both instances, *in vitro* Diltiazem Hydrochloride release profiles that were zero-order and pH-independent were obtained without chemical modification of the drug. Release rate from devices contained resin modulated or solubility modulated components showed zero order release. These approaches may be applied in general to extend osmotic pump technology to drugs with intrinsic water solubility that is too high or low for conventional osmotic pump formulations.

- **F.Theeuwes *et al.*,**[57] have developed oral osmotic drug delivery systems for Metoprololfumarate and Oxeprenolol succinate. *In vitro* testing confirmed that drug delivery corresponded closely to the theoretical release behaviour predicted from the physiochemical and membrane permeability characteristics for both Oxeprenolol and Metoprolol systems. *In vitro* release rates were also shown to be unaffected by pH, *in vitro* test procedures, dissolution media and long – term storage at different temperatures.

3. Scope of Work

In the present study, the possibility of developing an Oral Push-pull osmotic tablet for Losartan Potassium was explored. The system designed by using the basic design of Push-pull osmotic pump as push layer and pull layer consisting the polymer and drug respectively in the system. The investigation also aimed to use five different variables, the core and membrane variables. The type of osmogent, level of osmogent, the diameter of Orifice, the concentration of polymer and the thickness of the membrane are studied. These variables are optimized one after another by the dissolution profile.

The optimized formulation subjected to the test with different pH condition and agitational intensity. The developed systems were evaluated for the kinetics and pharmacopeial study as of oral tablets.

4. Plan of Work

1. Review of Literature
2. Pre-formulation
    a. Identification
    b. Drug Excipient interaction
    c. Variables to be investigated
3. Formula development and finalization
4. Optimization
5. Evaluation

    Evaluation of physical mixture

    - Bulk density
    - Angle of repose
    - Compressibility Index

    Evaluation of Tablets

    i. Weight variation
    ii. Hardness
    iii. Thickness
    iv. Friability
    v. Drug Content (Assay)
    vi. Drug release study

6. In-vitro characterization for optimized batch
    a. Effect of agitational intensity on drug release
    b. Effect of pH on drug release
7. Release Kinetics

8. Accelerated stability studies

5. Drug Profile

5.1 Losartan Potassium[58]

Losartan potassium also known as 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl) [1,1'-buphenyl] -4-yl]- 1H-imidazole-5-methanol mono-potassium salt, is a competitive AT_1 angiotensin II receptor antagonist and has the following formula:

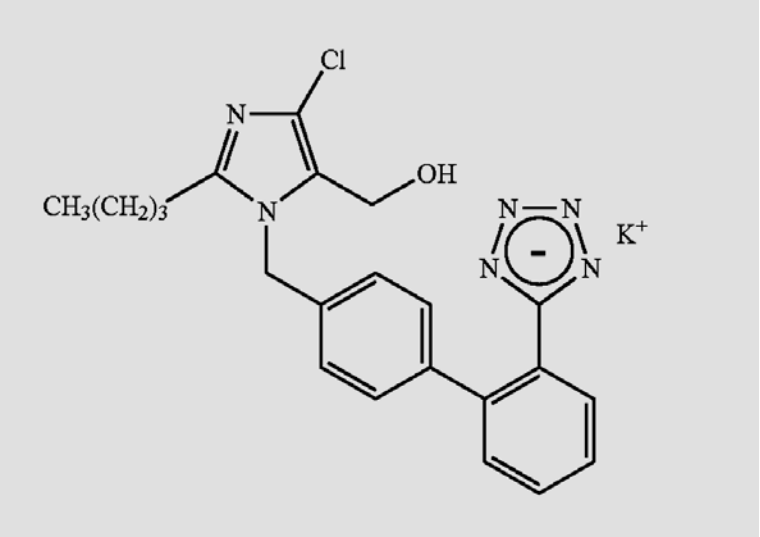

Fig.7 Chemical structure of Losartan potassium

Molecular formula	:	$C_{22}H_{23}ClN_6OK$
Molecular weight	:	461.01
Chemical Name	:	2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl) [1, 1'-buphenyl] -4-yl] - 1H-imidazole-5-methanol monopotassium
Appearance	:	A white to off-white crystalline powder.
Solubility	:	Freely soluble in water; soluble in isopropyl alcohol; slightly soluble in acetonitrile.
Half-life	:	2 hours

Therapeutic category	:	Anti-hypertensive
Storage	:	Store in a well closed container at controlled room temperature.

Losartan became the first non-peptide AT_1 antagonist approved by the U.S. Food and Drug Administration for the clinical use. It has been approved for the treatment of hypertension alone or in combination with other antihypertensive agents. Losartan may be administered orally as its mono-potassium salt.

5.2 Mechanism of Action[58]

Angiotensin II formed from angiotensin I in a reaction catalyzed by angiotensin converting enzyme, is a potent vasoconstrictor, the primary vasoactive hormone of the renin-angiotensin system and an important component in the pathophysiology of hypertension. It also stimulates aldosterone secretion by the adrenal cortex. Losartan and its principal active metabolite block the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor found in many tissues. There is also an AT_2 receptor found in many tissues but it is not known to be associated with cardiovascular homeostasis. Both losartan and its principal active metabolite do not exhibit any partial agonist activity at the AT_1 receptor and have much greater affinity (about 1000-fold) for the AT_1 receptor than for the AT_2 receptor. In vitro binding studies indicate that losartan is a reversible, competitive inhibitor of the AT_1 receptor. The active metabolite is 10 to 40 times more potent by weight than losartan and appears to be a reversible, non-competitive inhibitor of the AT_1 receptor.

5.3 Dosage and administration[59]

5.3.1 Adult Hypertensive Patients

Dosing must be individualized. The usual starting dose of Losartan potassium is 50 mg once daily, with 25 mg used in patients with possible depletion of intravascular volume e.g., patients treated with diuretics and patients with a history of hepatic impairment. Losartan potassium can be administered once or twice daily with total daily doses ranging from 25 mg to 100 mg.

If the antihypertensive effect measured at trough using once-a-day dosing is inadequate, a twice-a day regimen at the same total daily dose or an increase in dose may give a more satisfactory response. The effect of losartan is substantially present within one week but in some studies the maximal effect occurred in 3-6 weeks. No initial dosage adjustment is necessary for elderly patients or for patients with renal impairment, including patients on dialysis.

5.3.2 Paediatric Hypertensive Patients ≥ 6 Years of Age

The usual recommended starting dose is 0.7 mg/kg once daily (up to 50 mg total) administered as a tablet or a suspension. Dosage should be adjusted according to blood pressure response. Doses above 1.4 mg/kg (or in excess of 100 mg) daily have not been studied in pediatric patients. Losartan potassium is not recommended in pediatric patients < 6 years of age or in pediatric patients with glomerular filtration rate < 30 mL/min/1.73 m^2. Oral suspension is also available for pediatrics.

5.3.3 Hypertensive Patients with Left Ventricular Hypertrophy

The usual starting dose is 50 mg of Losartan potassium once daily. Hydrochloro-thiazide 12.5 mg daily should be added and/or the dose of Losartan Potassium should be increased to 100 mg once daily followed by an increase in hydrochlorothiazide to 25 mg once daily based on blood pressure response.

5.3.4 Nephropathy in Type 2 Diabetic Patients

The usual starting dose is 50 mg once daily. The dose should be increased to 100 mg once daily based on blood pressure response.

5.4 Pharmacokinetics[59]

5.4.1 General

Losartan potassium is an orally active agent that undergoes substantial first pass metabolism by cytochrome P450 enzymes and converted into active carboxylic acid and metabolite responsible for angiotensin II receptor antagonism that follows

losartan treatment. The terminal half - life of losartan is about 2 hours and of the metabolite is about 6-9 hours. The systemic bioavailability of losartan potassium is approximately 33% through oral administration. About 14% of an orally-administered dose of Losartan is converted to the active metabolite. Mean peak concentrations of Losartan and its active metabolite are reached in 1 hour and 3-4hours, respectively. Losartan and its active metabolite are highly bound to plasma proteins, primarily albumin, with plasma free fractions of 1.3% and 0.2%. Losartan crosses the blood brain barrier poorly confirmed by the studies in rats.

5.4.2 Special Populations

Paediatric

Pharmacokinetic parameters after multiple doses of losartan as a tablet to 25 hypertensive patients aged 6 to 16 years are shown in **Table 4** below:

Table: 4 Pharmacokinetic parameters determined after clinical examination

Pharmacokinetic parameter	**Adults given 50 mg once daily for 7days N=12**		**Age 6-16 given 0.7mg/kg once daily for 7 days N=25**	
	Parent	**Active Metabolite**	**Parent**	**Active Metabolite**
AUC_{0-24} (ng.h/mL)	442± 173	1685 ± 452	368 ± 169	1866 ± 1076
C_{MAX} (ng/mL)	224 ± 82	212 ± 73	141 ± 88	222 ± 127
$T_{1/2}$ (h)[b]	2.1 ± 0.70	7.4 ± 2.4	2.3 ± 0.8	5.6 ± 1.2
T_{PEAK} (h)[c]	0.9	3.5	2.0	4.1
CL_{REN} (mL/min)[a]	56 ± 23	20 ± 3	53 ± 33	17 ± 8

5.5 Contraindications[59]

Pregnancy, lactation, children with CreatinineClearance<30 ml/min/1.73 m^2

5.6 Adverse Drug Reaction[59]

Headache, dizziness, back pain, myalgia, respiratory tract disorders, asthenia / fatigue, first dose hypotension, rash, angioedema, neutropenia, GI disturbances, transient elevation of liver enzymes, impaired renal function, taste disturbances and hyperkalaemia

5.7 Drug Interactions[59]

Hypotensive effect of losartan is potentiated by diuretics and other antihypertensive drugs. Risk of hyperkalaemia increases with concomitant Acetylcholine Esterase (ACE) inhibitors, cyclosporine, potassium-sparing diuretics and K supplements. Hypotensive effect may be antagonised and increased risk of renal impairment when used with NSAIDs.

6. Excipients Profile

Polyethylene Oxide[60]

Synonyms	Polyox; polyoxirane; polyoxyethylene.
Description	White to off-white, free-flowing powder. Slight ammoniacal odor.
Molecular formula	$(CH_2CH_2O)n$
Chemical Name	Polyethylene oxide
Grades	WSR *N*-10,80,750,3000,12K, 60K, WSR 205, 301,1105, Coagulant
Molecular weight	Ranges from 100000 to 8000000
Viscosity	Dynamic.
Melting Point	65-70ºC
Functional Category	Muco-adhesive Coating agent, Tablet Binder, Thickening agent.
Solubility	Soluble in water and a number of common organic solvents such as acetonitrile, chloroform and methylene chloride. It is insoluble in aliphatic hydrocarbons, ethylene glycol and most alcohols.
Stability	Exposing to high temperature result in reduction in viscosity.
Storage	It should be stored in tightly sealed containers in a cool, dry place.
Incompatibilities	Polyethylene oxide is incompatible with strong oxidizing agents.
Applications	PEO can be used as tablet binder at concentrations of 5-85%. The higher molecular weight grades provide delayed drug release via the hydrophilic matrix approach. It is used in immediate- or sustained matrix formulations.

Lactose[61]

Synonyms	Anhydrous Lactose NF 60M, Anhydrous Lactose NF Direct Tableting, Lactopress Anhydrous, lactosum, lattioso; milk sugar, saccharum lactis, Super-Tab Anhydrous.
Description	Lactose occurs as white to off-white crystalline particles or powder. Several different brands of anhydrous lactose are commercially available which contain anhydrous β-lactose and anhydrous α-lactose. Anhydrous lactose typically contains 70–80% anhydrous β-lactose and 20–30% anhydrous α-lactose.
Molecular formula	$C_{12}H_{24}O_{11}$
Molecular weight	342.30
Chemical Name	*O*-β-D-galactopyranosyl-(1→4)-β-D-glucopyranose
pH	4.5–7.0 for 10 % w/v aqueous solution
Melting Point	201–202°C (for dehydrated α-lactose monohydrate)
Functional Category	Tablet and capsule diluent
Solubility	Soluble in water; sparingly soluble in ethanol (95%) and ether.
Stability	Under humid conditions (80% relative humidity and above), mold growth may occur. Lactose may develop of brown coloration on storage, the reaction being accelerated by warm, damp conditions. The purity of different lactose can vary and color evaluation may thus be important, particularly if white tablet are being formulated
Storage	It should be stored in well closed container

Incompatibilities	The presence of lactose anhydrous accelerate the hydrolysis of the ester and amidine groups
Applications	Anhydrous lactose is widely used in direct compression and as a tablet and capsule filler and binder. Anhydrous lactose can be used with moisture-sensitive drugs.

Colloidal Silicon Dioxide[62]

Synonyms	Aerosil, Colloidal silica, Fumed silica, Light anhydrous silicic acid, Silicic anhydride; Silicon dioxide fumed
Description	It is submicroscopic fumed silica with a particle size of about 15 nm. It is a light, loose, bluish-white-colored, odorless, tasteless, non-gritty amorphous powder.
Molecular formula	SiO_2
Molecular weight	60.08
Chemical Name	Silica
pH	3.5–4.4 (4% w/v aqueous dispersion)
Functional Category	Adsorbent, Anticaking agent, Emulsion stabilizer; Glidant; suspending agent, Tablet Disintegrant, Thermal stabilizer, Viscosity-increasing agent.
Solubility	Practically insoluble in organic solvents, water, and acids, except hydrofluoric acid; soluble in hot solutions of alkali hydroxide. Forms a colloidal dispersion with water.
Stability	Colloidal silicon dioxide is hygroscopic but adsorbs large quantities of water without liquefying.
Storage	It should be stored in a well-closed container.
Incompatibilities	Incompatible with diethylstilbestrol preparations
Applications	Its small particle size and large specific surface area give it desirable flow characteristics. It is also used as a thickening agent for topical preparations.

Talc[63]

Synonyms	Magil osmanthus, Magsil Star; powdered talc; purified much chalk, Purtalc, soapstone, Steatite
Description	It is very fine, white to grayish-white. Colored odorless, impalpable, unctuous, crystalline powder.
Molecular formula	$Mg_6(Si_2O_5)_4(OH)_4$
Chemical Name	Talc
pH	7.0 – 10.0 for a 20 % aqueous dispersion.
Melting Point	
Functional Category	Talcing agent, glidant; tablet and capsule diluent; tablet capsule lubricant
Solubility	Insoluble in water, organic solvent, dilute acid & alkalis.
Stability	Talc is a stable material and may be sterilized by heating at 160°C for not less than 1 hour. It may also be sterilized by exposure to ethylene oxide or gamma irradiation.
Storage	It should be stored in a well-closed container in a cool, dry place.
Incompatibilities	Incompatible with quaternary ammonium compounds
Applications	It is widely used in oral solid dosage forms as a glidant & diluent. It is used as a dusting powder in topical use. Additionally used to clarify liquids and mainly used in food and cosmetics products because of its lubricant properties.

Magnesium Stearate[64]

Synonyms	Magnesium octadecanoate, Octadecanoic acid, Magnesium salt of Stearic acid
Description	It occurs as a fine, white, precipitated or milled impalpable powder with a faint odor and a characteristic taste
Molecular formula	$C_{36}H_{70}MgO_4$
Molecular weight	591.34
Chemical Name	Octadecanoic acid magnesium salt
Melting Point	117 – 150ºC
Functional Category	Tablet and capsule lubricant
Solubility	Practically insoluble in ethanol, ether and water; Slightly soluble in warm benzene and warm Ethanol (95%)
Stability	It is a stable material
Storage	It should be stored in a well-closed container, in a cool, dry place.
Incompatibilities	Magnesium stearate cannot be used in products containing aspirin, some vitamins, and most alkaloidal salts Incompatible with strong acids, alkalis and iron salts.
Applications	It is primarily used as a lubricant in tablet and capsules in concentrations between 0.25 % and 5 %. It is widely used in cosmetic and food industry

7. Materials and Methods

7.1. Materials and Equipments Used

S.No.	Material Used	Source	Uses
1	**Losartan potassium**	Madras pharmaceuticals (P) Ltd.,	Anti-Hypertensive
2	**Polyethylene Oxide**	SigmaAldrich Ltd.,	Matrix Polymer
3	**Lactose**	LobaChemie Ltd.,	Diluent cum Osmotic agent
4	**Magnesium Stearate**	LobaChemie Ltd.,	Diluent
5	**Colloidal Silicon Dioxide**	LobaChemie Ltd.,	Adsorbent, Suspending agent
6	**Talc**	LobaChemie Ltd.,	Lubricant

Equipments Used

S.No.	Instruments	Brand
1	**Electronic weighing balance (Capacity: 10mg – 200mg)**	Axis, India
2	**Vernier callipers**	Mitutoyo, Japan
3	**Hardness tester**	Monsanto, China
4	**Tablet dissolution apparatus**	Electrolab, India
6	**UV Spectrophotometer**	Shimadzu UV 1061, Japan
7	**Compression machine-8 station**	Cadmach, India
8	**FT-IR Spectrophotometer**	Shimadzu corp., Japan.
9	**pH meter**	Digisun Electronics, India
10	**Hot air oven**	Pathak electrical works, India

7.2 Experimental Methods

7.2.1 Preformulation Studies

Preformulation studies are the first steps which focus on the physicochemical properties of new compound that could not affect drug performance and development of an efficacious dosage from. The objective of preformulation study is to develop a portfolio of information about the drug substance, so that this information is useful to develop a formulation.

Preformulation can be defined as investigation of physical and preformulation of drug substance alone and when combined with excipients. Preformulation investigations are designed to identify those physicochemical properties and excipients that may influence the formulation design, method of manufacture, and pharmacokinetic-biopharmaceutical properties of the resulting product.

7.2.2 Drug Excipient Interaction studies

Drug excipient interaction study was performed in pre-formulation stage to assess the possible incompatibilities of the Active Pharmaceutical Ingredients with the excipients in the process of development of a solid dosage form. This interaction can be found out by performing thermal analysis of the drug and excipients using Differential Scanning Calorimetery (DSC) at the recommended conditions. The variations in the DSC thermograms of the pure drug were compared with the DSC thermograms of the drug and excipient mixture. The incompatibilities can be identified by variations in the corresponding enthalpies. The DSC analysis was performed in heat flow rate of 10ºC/ min in the temperature range from 30 ºC to 450 ºC.

7.2.3 Raw Material Analysis

Appearance	**:**	A white to off-white crystalline powder
Solubility	**:**	Freely soluble in water; Soluble in isopropyl alcohol; slightly soluble in acetonitrile.
Assay	**:**	100.0mg of Losartan Potassium working standard was accurately weighed and transformed into 100ml volumetric flask and the volume is made up with purified water. Take 1ml of the above solution and transfer into 100ml volumetric and make up the volume with purified water and mix.
Identification Test	**:**	Infrared spectra, Heavy metals, sulphated ash and loss on Drying were carried out as per IP 2010.

7.2.4 Pre-Compression Parameters

7.2.4.1 Bulk Density[65]

The powder sample (blend) under test was screened through sieve #18 and the sample equivalent to 20g was accurately weighed and filled in a 100ml graduated cylinder and the powder was leveled and the unsettled volume (V_0) was noted. The bulk density was calculated in g/cm^3 by the formula,

$$\text{Bulk density } (\rho_0) = \frac{M}{V_0}$$

where,

M = mass of powder taken

V_0= apparent untapped volume

7.2.4.2 Angle of Repose[65]

Angle of repose of the granules was determined by the height cone method. A funnel was fixed to a desired height and granules were filled in it. They were

allowed to flow down on a graph paper fixed on a horizontal surface and angle of repose was calculated using the formula given in equation,

$$\text{Tan } \theta = \frac{2h}{D}$$

where, h and Dare height and diameter of the pile respectively. The specifications of angle of repose were given in **Table: 5.**

Table: 5 Flow of Powders with Angle of Repose values

Angle of repose (degrees)	Type of flow
< 20	Excellent
20-30	Good
30-34	Passable*
> 40	Very poor

*May be improved by glidant

7.2.4.3 Compressibility Index[65]

Based on the poured density and tapped density, the percentage compressibility of the granules was computed using the Carr's compressibility index by the formula and the Carr's index value and its specifications are given in **Table: 6.** $Carr's\ index\ (\%) = \frac{poured\ density - tapped\ density}{Poured\ Density}\ X\ 100$

Table: 6 Flow of Powders with Carr's Index values

Carr's index (%)	Type of flow
5-15	Excellent
12-16	Good
18-21	Fair to passable
23-35	Poor
33-38	Very poor
> 40	Extremely poor

7.3 Formulation of Tablets

The core tablet consists of bilayer, the upper drug layer and lower push layer which compressed directly into the tablet form. The push layer was first filled in the die cavity and compacted using 16/32 inch deep concave punches. Then the drug layer is laid into the die cavity and compacted. Finally the bilayer composition was compressed with maximum pressure. The compression was carried out by using rotary tablet compression machine with 8 stations. The formula for drug layer and push layer is given in **Table: 7**.

Table: 7 Formula for Drug layer and push layer

Drug Layer Ingredients*	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
Drug	100	100	100	100	100	100	100	100	100	100	100	100
Aerosil	5	5	5	5	5	5	5	5	5	5	5	5
Talc	16	16	16	16	16	16	16	16	16	16	16	16
Magnesium Stearate	5	5	5	5	5	5	5	5	5	5	5	5
Lactose	-	50	100	150	100	100	100	100	100	100	100	100
Nacl	100	-	-	-	-	-	-	-	-	-	-	-
Push Layer Ingredients*	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
PEO	100	100	100	100	100	100	100	200	50	200	200	100
Aerosil	5	5	5	5	5	5	5	5	5	5	5	5
Talc	16	16	16	16	16	16	16	16	16	16	16	16
Magnesium Stearate	5	5	5	5	5	5	5	5	5	5	5	5
Lactose	-	50	100	150	100	100	100	100	100	100	100	100
Nacl	100	-	-	-	-	-	-	-	-	-	-	-

**All ingredients were taken in milligram*

7.3.1 Coating and Drilling

The bilayer tablets were coated with a 4% w/w cellulose acetate in acetone semipermeable membrane using pan coater. The coated tablets were drilled mechanically with different orifice diameter by using different drill bits.

The coating conditions are indicated as follows:

Pan specification	:	stainless steel, spherical, 300 mm diameter
Pan rotating	:	18 rpm.
Spray rate	:	3ml/min.
Drying	:	by a heat gun

Coated tablets were dried over night at 40ºC in a hot air oven. The tablets were obtained thickness by concurrent coating with the coating solution.

7.4 Optimization of Variables

Five variables were taken into consideration to optimize the release of drug from the osmotic system. The five variables taken for optimization were osmogent type, osmogent concentration, orifice diameter, polymer concentration and membrane thickness. These four parameters were taken for optimization as these have great influence on drug release from the osmotic system. Optimization was carried out based on the *in vitro* drug release profile for each parameter. **Table: 8** represents the optimization process based on the drug release profile.

Table: 8 Optimization Process for independent formulation variables

Formulation	Osmogent Type	Osmogent Concentration (mg)	Orifice diameter (µm)	Polymer Concentration (mg)	Coating Thickness (%)
F1	Sodium Chloride	200	850	100	12 %
F2	Lactose	200	850	100	12 %
F3	Optimized	100	850	100	12 %
F4	Optimized	300	850	100	12 %
F5	Optimized	Optimized	450	100	12 %
F6	Optimized	Optimized	550	100	12 %
F7	Optimized	Optimized	250	100	12 %
F8	Optimized	Optimized	Optimized	200	12 %
F9	Optimized	Optimized	Optimized	50	12 %
F10	Optimized	Optimized	Optimized	Optimized	10%
F11	Optimized	Optimized	Optimized	Optimized	15%
F12	Optimized	Optimized	Optimized	Optimized	Optimized

7.4.1 Effect of Osmogent Type

To investigate the effect of osmotic agent type on the drug release two different types of osmotic agent were chosen for this study. Sodium chloride and lactose were selected as models for this investigation. The two osmotic agents were taken in same concentration and the release of drug from these two systems was investigated. The osmotic agents were taken in both the upper and lower layer of the tablet. The formula for the F1 and F2 formulation were given in the **Table: 7**. The drug releases of both the formulations were carried out as the same procedure.

7.4.2 Effect of Osmogent Concentration on Drug Release

In order to study the effect of osmogent concentration on the drug release, tablets with different concentrations of osmogent were prepared. The osmogent concentrations taken for investigation were100, 200 and 300 mg being all other variables were kept constant. The percentage releases of the drug of different formulations were recorded.

7.4.3 Effect of Delivery Aperture on Drug Release

To investigate the effect of aperture on the drug release, the coated tablets were drilled manually with different orifice sizes 250,450, 550 and 850 µm. The percentage release of the drug was studied and compared.

7.4.4 Effect of Polymer Concentration on Drug Release

To study the effect of polymer concentration on drug release, tablets with different concentration of polyethylene oxide corresponding to the drug were prepared. Different polymer concentration taken into account for this study was 50mg, 100mg and 200mg. The tablets with three different polymer concentrations were prepared and coated being other variables were kept constant.

7.4.5 Effect of Membrane Thickness on Drug Release

The effect of coating thickness, the core tablets were coated with three different level of 4% w/w cellulose acetate in acetone. The coating thickness is increased to three levels of tablet weight gain, such as 10, 12 and 15% w/w of the core tablet.

7.5 Evaluation of Tablets

The compressed tablets were evaluated for the following tests and the results are tabulated in **Table: 11**.

7.5.2 Thickness

The tablet thickness is an important factor which is to be investigated during packaging. At constant compressive load, thickness of tablets varies with changes in die fill, particle size distribution and packing of the particle mix being compressed. Tablet thickness of all the formulations was measured using verniercalipher and the reading was recorded.

7.5.3 Hardness

Hardness is defined as the force required for breaking a tablet in a diametric compression test. This parameter is important to know that the tablet has sufficient strength to withstand mechanical shocks of handling in manufacturing, packaging and shipping. Tablet hardness was measured using a Monsanto hardness tester.

7.5.4 Assay of Losartan Potassium by UV-Spectrophotometer

Standard Preparation

100.0mg of Losartan Potassium working standard was accurately weighed and transformed into 100ml volumetric flask and the volume is made up with purified water. Take 1ml of the above solution and transfer into 100ml volumetric and make up the volume with purified water and mix.

Sample Preparation

Twenty tablets were weighed and powdered. 110 mg of powdered tablet (equivalent to 100 mg of Losartan Potassium) weighed and transferred into 100ml volumetric flask and the volume is made up with purified water. Take 5ml of the above solution and transfer it into 100ml volumetric and make up the volume with purified water and mix. The solution was filtered through 0.45 µm membrane filter and measured with UV-Spectrophotometer at 235 nm.

Calculation

$$\frac{A_{sam}}{A_{std}} \times \frac{W_1}{100} \times \frac{1}{100} \times \frac{100}{W_2} \times \frac{100}{5} \times \frac{P}{100} \times \frac{\text{Avg. Wt.}}{L.C} \times 100$$

A_{sam} → Absorbance of the sample preparation

A_{std} → Absorbance of the standard preparation

W_1 → Weight in mg of Losartan potassium working standard

W_2 → Weight in mg of Losartan potassium sample.

P → Percentage purity of Losartan Potassium of working standard

L.C → Label claim of Losartan potassium.

Avg. Wt → Average weight of tablet.

7.5.5 In vitro Drug Release

Chemicals and Reagents

1. Purified water.
2. Potassium dihydrogen orthophosphate.
3. Sodium hydroxide.

Dissolution test Condition

Model	:	Electrolab Dissolution
Apparatus	:	USP type II (paddle)
Medium	:	pH 6.8 phosphate buffer
Medium Volume	:	900ml
Temperature	:	37ºC
Rotation speed	:	100 rpm
Sampling time	:	2, 4, 6, 8, 12 and 24hour.

UV Parameters

Path Length	:	1mm
Wave length	:	235 nm
Mode	:	Photometric

- **Preparation of pH 6.8 Phosphate Buffer**

6.8g of Potassium Di-hydrogen Orthophosphate and 5 M of sodium hydroxide was mixed in purified water. Then the solution is made up to 1000ml with purified water. The pH of the solution was adjusted to 6.8 ± 0.05.

- **Standard Preparation**

50.0mg of Losartan Potassium working standard was accurately weighed and transformed into 100ml volumetric flask and the volume is made up with purified water. Take 1ml of the above solution and transfer into 100ml volumetric and make up the volume dissolution medium.

- **Sample Preparation**

Dissolution apparatus was set as per above parameters. One tablet was placed in each of the six dissolution basket and the apparatus was allowed to attain

the set protocol. The dissolution apparatus was operated. At the end of specified sampling time, 5ml of the dissolution medium were withdrawn and filtered through 0.45µm.After each sampling time the medium was replaced with fresh solution.1ml of the filtrate from each vessel was separately diluted to 25 ml with dissolution medium. The absorbance of the drug was measured at 235 nm.

The percentage of drug release was calculated by using the formula

$$\% \text{ Drug Release} = \frac{A_{sam}}{A_{std}} \times \frac{W_1}{100} \times \frac{1}{100} \times \frac{900}{W_2} \times \frac{P}{100} \times 100$$

A_{sam} → Absorbance of the sample preparation

A_{std} → Absorbance of the standard preparation

W_1 → Weight in mg of Losartan potassium working standard

W_2 → Weight of one tablet.

P → Percentage purity of Losartan Potassium of working standard

L.C → Label claim of Losartan potassium.

7.5.6 Effect of Agitational Intensity

In order to investigate the effect of agitational intensity of the release media, drug release of the optimized formulation were carried out in the dissolution apparatus USP II at different rotational speeds. The rotational speeds taken for the investigation were 50, 100 and 150 rpm. Samples were withdrawn at 2, 4, 6, 8, 12 and 24 hour of different time intervals. Collected samples were filtered and analysed. The percentage cumulative drug release of the optimized formulation at various rotational speeds was plotted and the results were compared.

7.5.7 Effect of pH on Drug Release

In order to study the effect of pH and to assure a reliable performance of the developed formulations independent of pH, release studies of the optimized formulations were conducted in media of different pH 1.2, pH 6.8 and pH change method in which the release media was simulated gastric fluid for first 2 h and then followed by pH 6.8. The samples of five millilitres were withdrawn at pre-determined intervals and analysed after filtration. The percentage cumulative drug release of optimized formulations at various pH was plotted and compared.

7.6 Release Kinetics

The kinetics of drug release for the controlled release osmotic pump tablet was studied. The *in vitro* dissolution data of the optimized formulation was fitted into various kinetic models. The first order equation describes that the release is concentration dependent. According to Higuchi model, the drug release from insoluble matrix is directly proportional to square root of time and is based on Fickian diffusion. Drug release data obtained was applied to different drug release models in order to establish the drug release mechanism and kinetics. Best goodness of fit test (R^2) was taken as criteria for selecting the most appropriate model.

7.6.1 Zero Order Equation

The graph was plotted as percentage drug released against time in hours. Zero order kinetics can be expressed by equation (5)

$$\mathbf{C = K_0 t} \qquad \mathbf{(5)}$$

where,

K_0 = Zero order constant in concentration/time.

t = Time in hours.

The graph would give a straight line with a slope equal to K_0 and intercept the origin of the axis.

7.6.2 First Order Kinetics

The graph was plotted as log % cumulative drug remaining against time in hours. The equation for first order kinetics is given in equation (6)

$$\mathbf{Log\ C = Log\ C_0 - Kt / 2.303} \qquad \mathbf{(6)}$$

Where,

C_0 = Initial concentration of drug

K = First order constants

t = Time in hours.

7.6.3 Higuchi Kinetics

The graph was plotted as % Cumulative drug released against square root of time. Higuchi kinetics can be calculated by equation (7)

$$\mathbf{Q = Kt^{1/2}} \qquad \mathbf{(7)}$$

where,

K = constant reflecting design variable system

t = time in hours.

Hence drug release rate is proportional to the reciprocal of square root of time. If the plot yields a straight line and the slope is one, then the particular dosage form is considered to follow Higuchi kinetics of drug release.

7.6.4 Hixson – Crowell equation

Hixson – Crowell equation is plotted to evaluate the drug release with changes in the surface area and the diameter of particles. The graph was plotted by cube root of % drug remaining against time in hours.

$$Q_0^{1/3} - Qt^{1/3} = K_{HC}\, Xt \qquad (8)$$

Where,

Qt = Amount of drug released in time‘t’.

Q_0 = Rate constant for Hixson – Crowell equation.

7.6.5 Koresmeyer – Peppas equation

Peppas equation is plotted by using log cumulative % of drug released against time.

$$M_t / M\alpha = Kt^n \qquad (9)$$

$$\text{Log } M_t / M\alpha = \log K + n \log t \qquad (10)$$

Where,

M_t / Mα = Fraction of drug released at time’t’.

T = Release time

K = kinetic constant (incorporating structural and geometric characteristics of preparation).

n = Diffusional exponent indicative of the mechanism of drug release.

- If n value is 0.5 or less, the release mechanism follows “fickian diffusion” and higher values of $0.5 < n > 1$ for mass transfer follow a non-fickian model (anomalous transport).
- The drug release follows zero-order drug release and case II transport if the value is 1.
- For the values of n higher than 1, the mechanism of drug release is regarded as super case II transport. This model is used to analyse the release of pharmaceutical polymeric dosage forms when the release mechanism is not known or more than one type of release was involved. The n value could be

obtained from slope of the plot of log cumulative % drug released Vs log time.

7.7. Stability Studies

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light and to establish a retest for the drug substance or a shelf life for the drug product and recommended storage conditions. Stability of a drug is defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutical and toxicological specifications. The following storage conditions for stability studies are followed as per ICH guidelines.

Table: 9 Storage conditions for stability studies as per ICH guidelines

Type of Study	Storage conditions
Long term	25ºC±2ºC / 60% RH ± 5%RH
Intermediate	30ºC±2ºC / 65% RH ± 5%RH
Accelerated	40ºC±2ºC / 75% RH ± 5%RH

The final tablets were subjected to accelerated stability studies. The tablets were kept in stability chamber. The samples were analyzed at 0, 1 and 2 months' time points. The data was analysed for any significant changes from the initial data. The following tests were performed

i. Test for physical parameters.
ii. Assay
iii. *In-vitro* dissolution study.

The conditions to carry out stability studies were given in the **Table 9.**

8.0 Results

8.1 Preformulation Studies

8.1.1 Drug Excipient Compatibility Studies

Conditions

Heat Flow rate **:** 10ºC / min**.**

Temperature range **:** 30 ºC - 450 ºC

The drug excipient interaction was investigated by Differential Scanning Calorimetry, one of the fast evaluating methods to study the drug excipient interactions. The Fig.10 and Fig.11 depicts the thermograms of the pure Losartan Potassium and Losartan Potassium with the excipients expressing that there was no significant variations was observed during the Thermal analysis proved that there was no interaction between the drug and the excipients.

Table: 10 Raw Material Analyses

Tests	Specifications	Observation
Description	A white to off-white crystalline powder	Off-white crystalline powder
Solubility	Freely soluble in water, soluble in isopropyl alcohol, slightly soluble in acetonitrile	Complies
Identification	The Infrared spectrum of the should match with the standard spectrum	Complies
Heavy metals	NMT 20 ppm	Complies
Assay	NLT 98.0 % and NMT 102%	99.8%

Conditions: RT 40ºC ± 2ºC and RH 75% ± 5%

Table: 11 Physical Observations

Drug + Excipient	Parameter	Observation		Comments
		Initial	After 30 days	
Losartan Potassium + PEO	Colour Change	No colour change	No colour change	Compatible
Losartan Potassium + Lactose	Colour Change	No colour change	No colour change	Compatible
Losartan Potassium + Aerosil	Colour Change	No colour change	No colour change	Compatible
Losartan Potassium + Magnesium Stearate	Colour Change	No colour change	No colour change	Compatible
Losartan Potassium + Talc	Colour Change	No colour change	No colour change	Compatible
Losartan Potassium + Cellulose Acetate	Colour Change	No colour change	No colour change	Compatible
Losartan Potassium + Acetone	Colour Change	No colour change	No colour change	Compatible

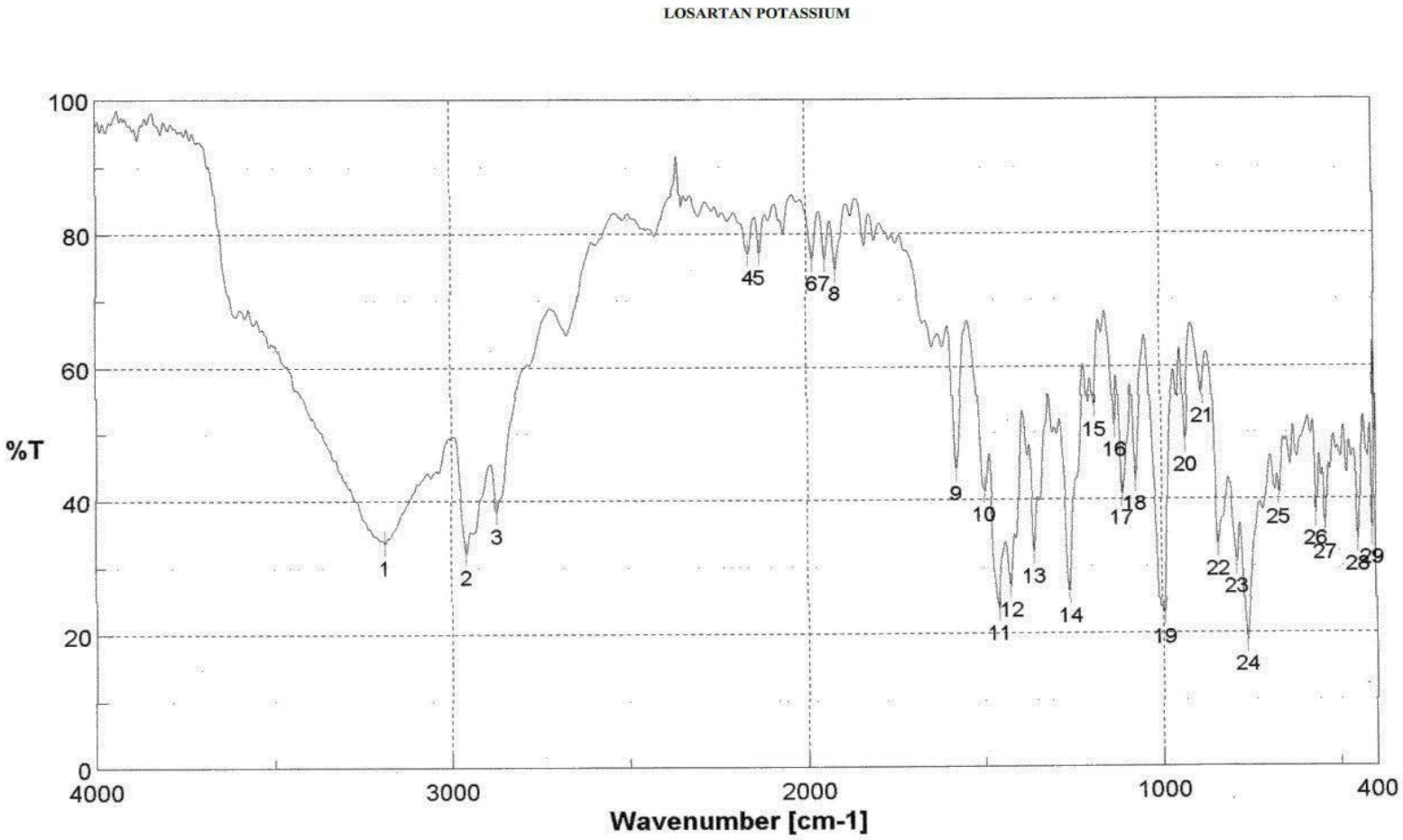

Fig.8 Infrared spectrum of Losartan potassium working standard

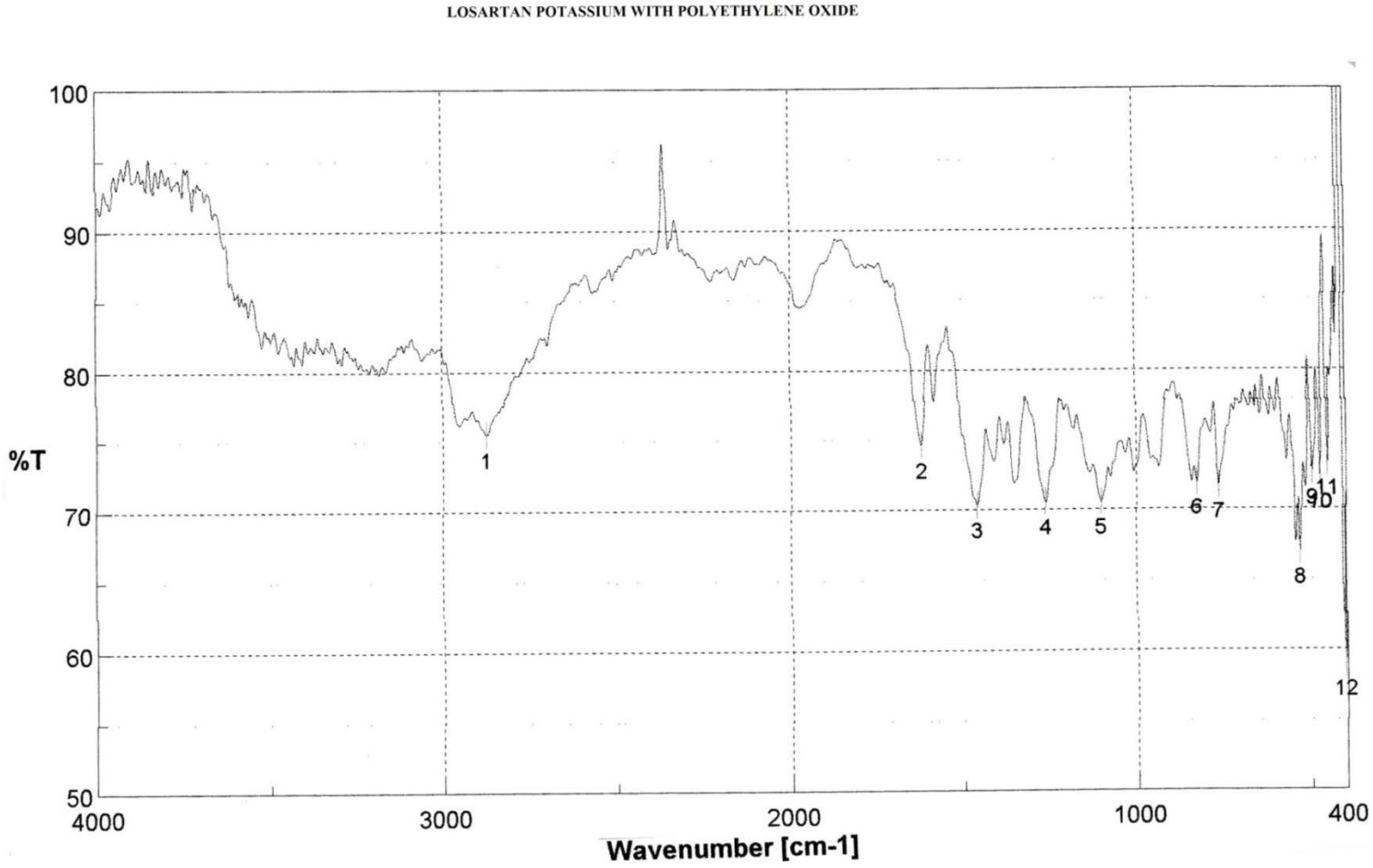

Fig.9 Infrared spectrum for mixture of Losartan Potassium and Polyethylene Oxide

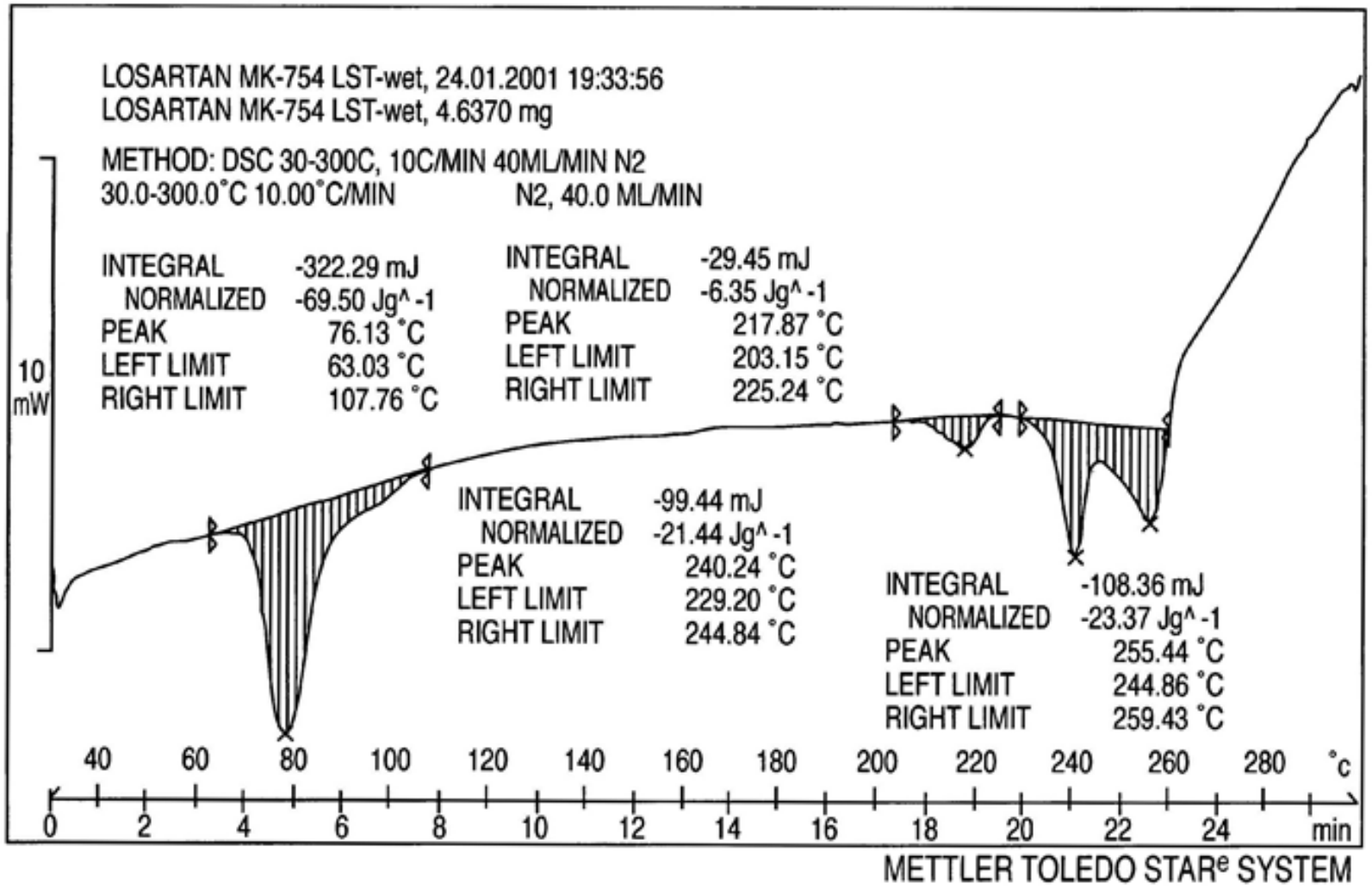

Fig. 10 DSC Thermogram of pure Losartan Potassium

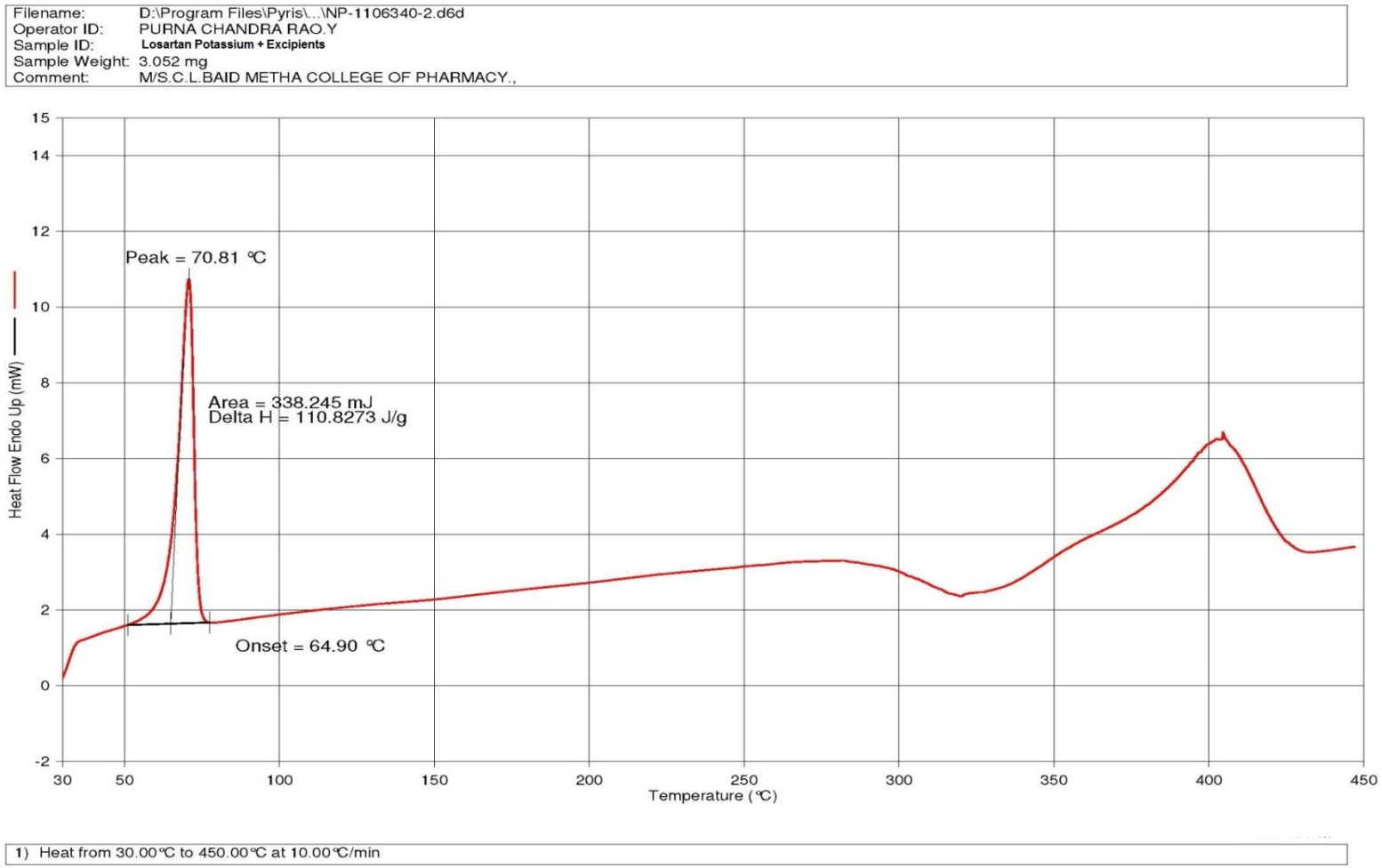

Fig.11 DSC Thermogram of Losartan Potassium with Excipients.

Table: 12 Evaluation of Physical mixtures

Formulation Code	Bulk Density g/ml	Tapped Density g/ml	Compressibility Index %	Angle of Repose
F_1	0.42 ± 0.02	0.49 ± 0.04	14.28 ± 0.10	24.50 ± 0.16
F_2	0.44 ± 0.04	0.51 ± 0.06	13.72 ± 0.04	26.68 ± 0.23
F_3	0.43 ± 0.06	0.50 ± 0.02	14.01 ± 0.03	25.54 ± 0.45
F_4	0.43 ± 0.05	0.49 ± 0.03	14.28 ± 0.05	28.56 ± 0.13
F_5	0.41 ± 0.03	0.48 ± 0.05	14.31 ± 0.03	25.87 ± 0.38
F_6	0.43± 0.06	0.49 ± 0.06	12.24 ± 0.08	28.09 ± 0.41
F_7	0.41 ± 0.09	0.49 ± 0.02	14.76 ± 0.04	25.34 ± 0.26
F_8	0.44 ± 0.06	0.50 ± 0.03	12.10± 0.06	27.56± 0.38
F_9	0.42 ± 0.04	0.50 ± 0.02	13.56 ± 0.03	26.54 ± 0.24
F_{10}	0.43 ± 0.06	0.49 ± 0.04	12.67 ± 0.07	27.80 ± 0.19
F_{11}	0.42 ± 0.05	0.48 ± 0.03	14.52 ± 0.03	24.17 ± 0.33
F_{12}	0.42 ± 0.06	0.49 ± 0.06	14.08 ± 0.02	26.16 ± 0.46

Mean ± SD (n = 6)

8.2 Evaluation of Tablets

Table: 13 Evaluation of Uncoated Tablets

Formulation code	Thickness* (mm)	Hardness* Kg/cm^2	Assay# (%)
F_1	5.02 ± 0.032	6.02 ± 0.065	99.78 ± 0.552
F_2	5.22 ± 0.023	6.63 ± 0.043	99.23 ± 0.412
F_3	5.36 ± 0.016	6.53 ± 0.098	98.78 ± 0.312
F_4	4.89 ± 0.026	6.32 ± 0.023	101.34 ± 0.167
F_5	5.86 ± 0.015	6.32 ± 0.045	99.78 ± 0.341
F_6	5.41 ± 0.043	6.67 ± 0.021	100.76 ± 0.213
F_7	5.45 ± 0.021	6.45 ± 0.067	98.59 ± 0.541
F_8	4.94 ± 0.085	6.43 ± 0.089	98.64 ± 0.257
F_9	5.34 ± 0.021	6.45 ± 0.031	99.21 ± 0.364
F_{10}	5.54 ± 0.045	6.00 ± 0.041	99.65 ± 0.421
F_{11}	5.23 ± 0.034	5.94 ± 0.054	98.32 ± 0.231
F_{12}	4.92 ± 0.078	6.02 ± 0.032	98.54 ± 0.478

*** Mean ± SD (n = 6) #Mean ± SD (n = 3)**

8.3 Optimization of variables

8.3.1 Effect of Osmogent Type

The release rate of the system containing two different osmotic agents was studied and the results are recorded in **Table: 14**. **Fig. 12** shows the comparison of release rate between the two types of osmotic agents.

8.3.2 Influence of Osmotic agent Concentration on Drug Release

The effect of osmotic agent concentration on drug release was studied and the results are tabulated in **Table: 15**. The osmotic agent of three different concentration chosen for the study was completed and the results are compared. **Fig. 13** illustrates the release rate of the drug from the system.

8.3.3 Influence of Orifice diameter on Drug release

The effect of orifice diameter was investigated by drilling orifice with different diameter. The results were recorded and the release rates of drug through different orifices were compared. The percentage drug release for corresponding delivery orifices were given in **Table: 16**. The comparison of the release is shown in the **Fig. 14**.

8.3.4 Effect of polymer concentration on drug release

The effects of polymer concentration on drug release were inspected and the results were given in the **Table: 17**. The polymer present in the push layer which is of high molecular weight is act as a swelling agent which able to control the release of the drug for a prolonged period of time. The hydrogel formation of the polymer at the end of dissolution was confirmed by latex formation. The results were compared and represented in **Fig. 15.**

8.3.5 Influence of Membrane Thickness on Drug Release

The effect of membrane thickness on drug release was investigated and the results were given in the **Table: 18**. The drug release is inversely proportional to the membrane thickness. The results were shown in **Fig. 16.**

8.3.6 Effect of Agitational Intensity

The release from the optimized formulation is found to be independent of the agitational intensity. The graph plotted in **Fig. 17** shows that there is no significant difference in drug release under different agitations. **Table: 19** represent the influence of agitational intensity on drug release.

8.3.7 Effect of pH on Drug Release

Figure showed release of drug from an optimized formulation in pH (1.2); pH change method and pH 6.8 respectively. The results showed that the release

profile is same in all the media, hence the optimized formulation showed independent release depicted in **Fig. 18**.

Table: 14 Release of Losartan from different type of Osmogent.

Time (h)	Osmogent Type	
	Sodium Chloride	**Lactose**
0	0.00 ± 0.00	0.00 ± 0.00
2	27.16 ± 0.05	37.54 ± 0.14
4	35.74 ± 0.65	45.54 ± 0.34
6	46.29 ± 0.23	56.08 ± 0.21
8	68.6 6± 0.37	62.43 ± 0.34
12	93.37 ± 0.45	76.21 ± 0.18
24	-	98.23 ± 0.54

Mean ±SD (n = 6)

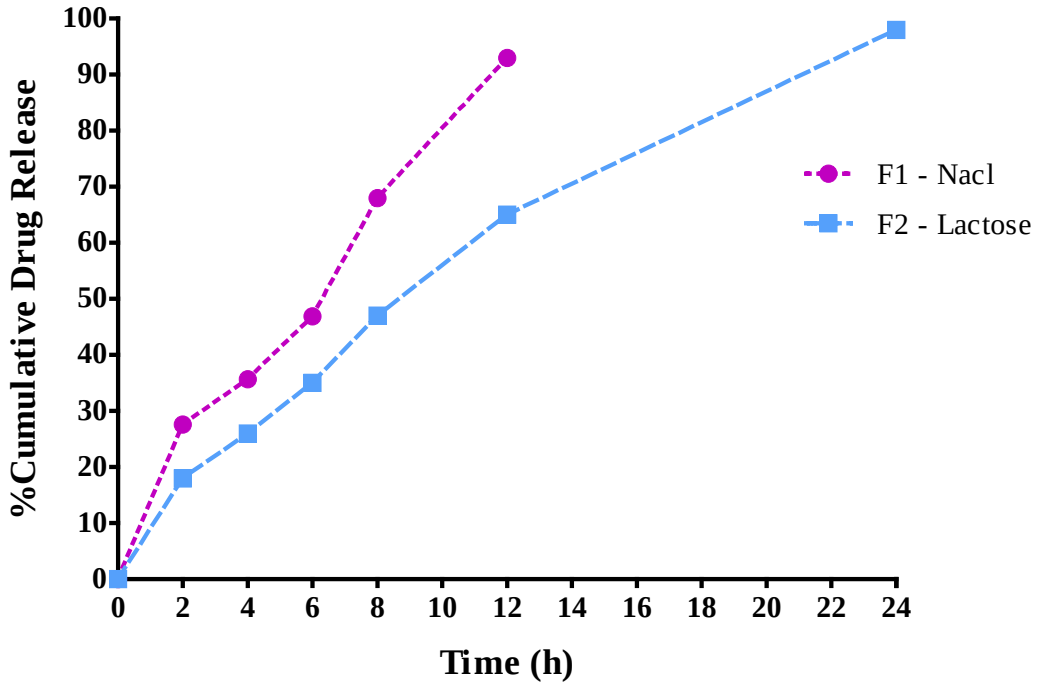

Fig.12 *In vitro* dissolution profile of Losartan from various Osmogent

Table: 15 Influence of Osmotic agent concentration on drug release

Time (h)	Osmotic agent Concentration		
	F3 (100mg)	F2 (200mg)	F4 (300mg)
0	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
2	8.23 ± 0.30	14.23 ± 0.43	28.76 ± 0.43
4	14.56 ± 0.23	24.50 ± 0.36	48.27 ± 0.12
6	26.43 ± 0.50	36.21 ± 0.46	68.20 ± 0.36
8	37.65 ± 0.42	48.20 ± 0.67	77.23 ± 0.45
12	48.21 ± 0.32	66.54 ± 0.43	90.43 ± 0.32
24	70.32 ± 0.68	97.64 ± 0.51	-

Mean ± SD (n = 6)

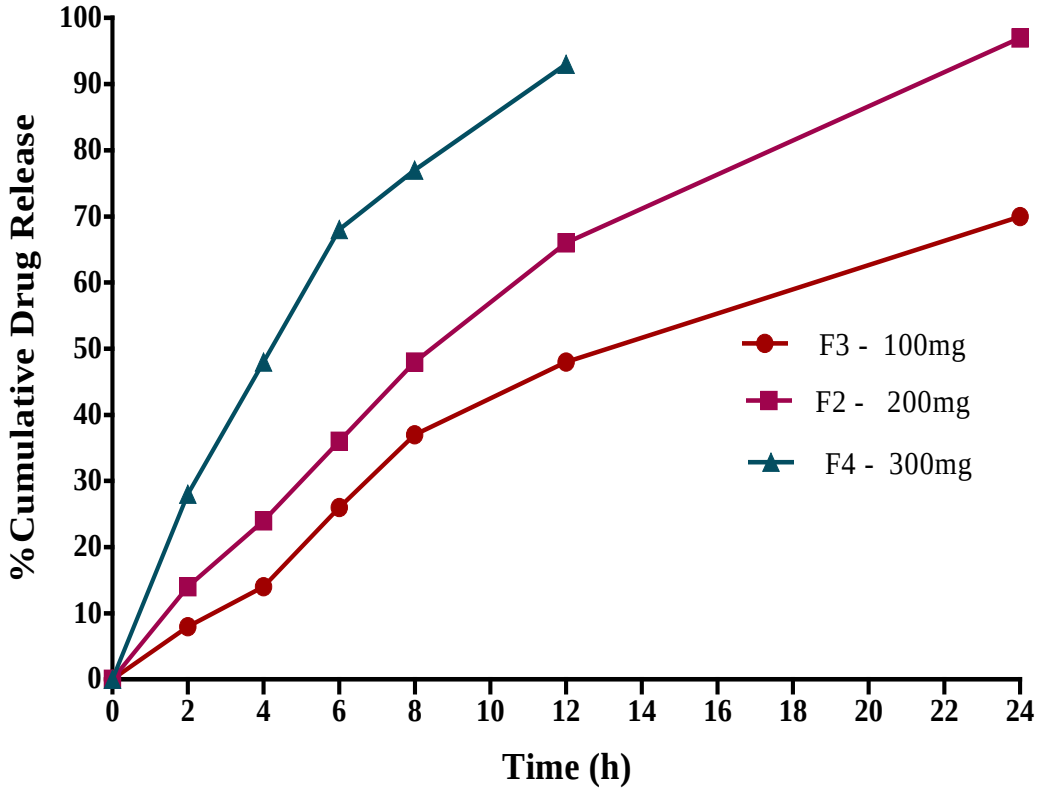

Fig.13 *In vitro* dissolution profile of Losartan from various concentrations of Osmogent

Table: 16 Influence of Orifice diameter on drug release

Time (h)	Orifice diameter			
	250 µm	450 µm	550 µm	850 µm
0	0.00± 0.00	00.00 ± 0.00	00.00 ± 0.00	00.00 ± 0.00
2	10.23 ± 0.13	26.42 ± 0.43	39.63 ± 0.34	45.21 ± 0.45
4	25.43 ± 0.25	37.21 ± 0.41	51.43 ± 0.43	58.43 ± 0.39
6	36.21 ± 0.43	46.32 ± 0.54	67.42 ± 0.23	67.42 ± 0.32
8	44.43 ± 0.46	59.17 ± 0.34	78.21 ± 0.46	82.24 ± 0.21
12	55.24 ± 0.21	78.32 ± 0.12	89.32 ± 0.41	90.12 ± 0.12
24	72.76 ± 0.45	98.21± 0.23	96.43 ± 0.25	-

Mean ± SD (n = 6)

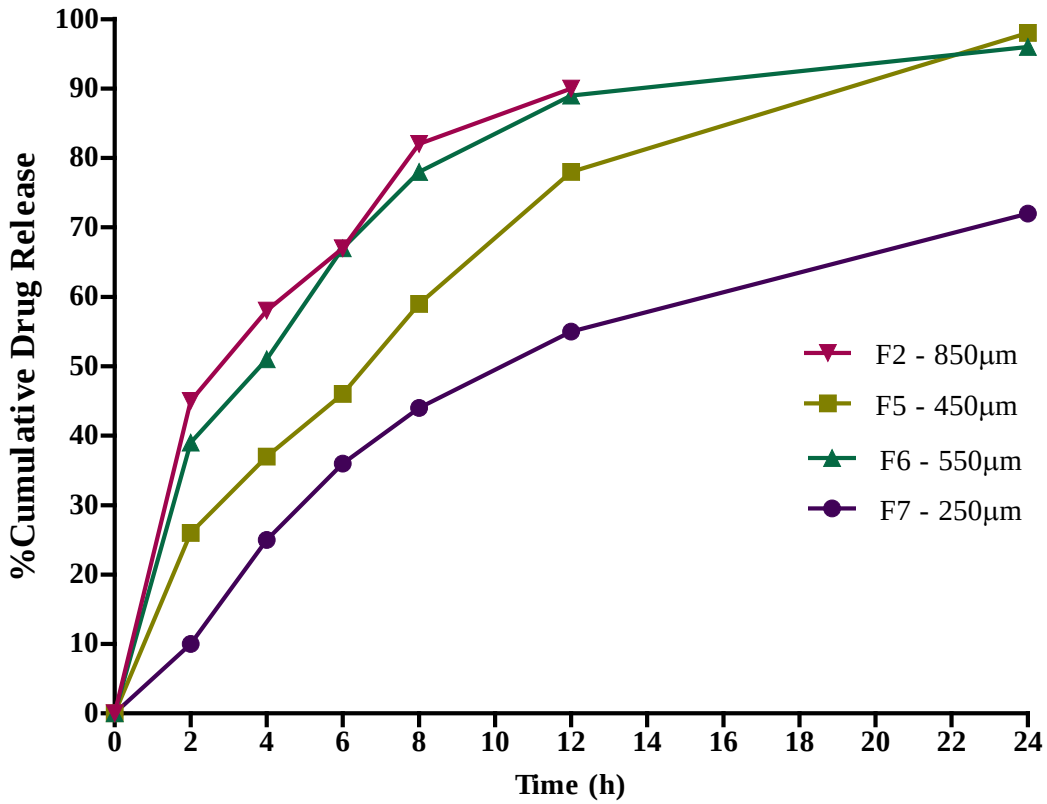

Fig.14 Effect of Orifice Diameter on Drug release

Table: 17 Effect of polymer concentration on drug release

Time (h)	Polymer Concentration		
	F9 (50mg)	F5 (100mg)	F8 (200mg)
0	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
2	22.12 ± 0.21	12.32 ± 0.25	9.32 ± 0.25
4	42.12 ± 0.28	26.32 ± 0.21	19.43 ± 0.53
6	58.21 ± 0.21	39.62 ± 0.89	24.41 ± 0.43
8	65.67 ± 0.39	46.32 ± 0.40	35.62 ± 0.74
12	93.21 ± 0.41	62.21 ± 0.81	54.23 ± 0.41
24	98.12 ± 0.32	98.45 ± 0.32	70.02 ± 0.25

Mean ± SD (n = 6)

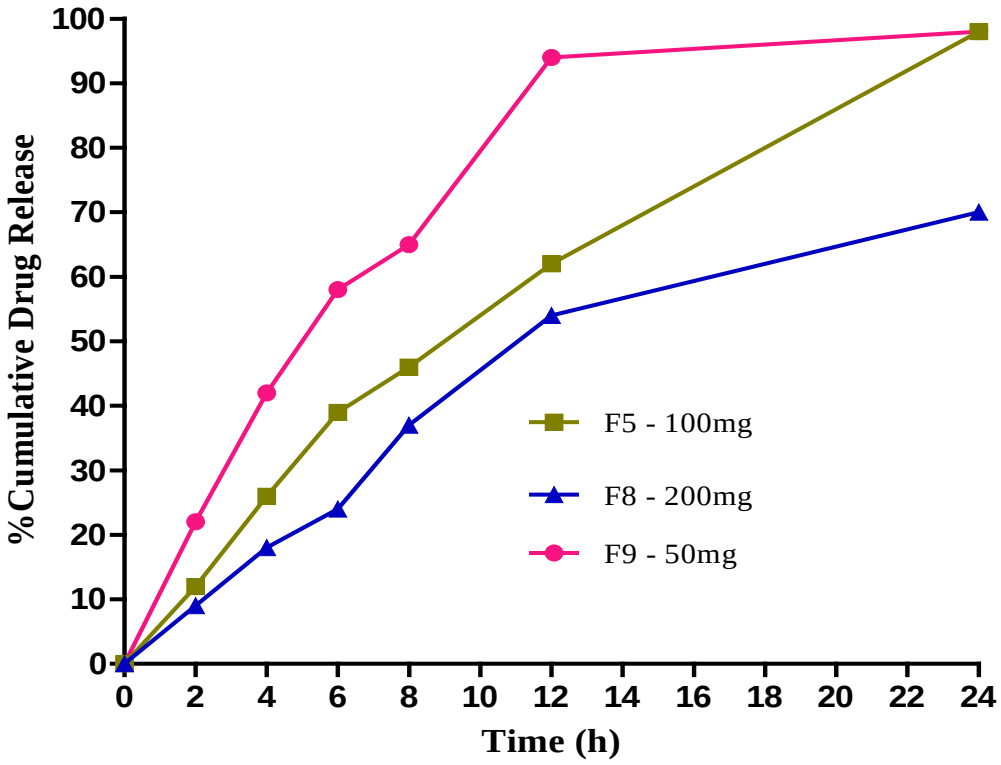

Fig.15 Influence of polymer concentration on Drug release

Table: 18 Influence of membrane thickness on Drug release

Time (h)	Membrane Thickness		
	10%w/w	**12% w/w***	**15% w/w**
0	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
2	18.21 ± 0.45	12.32 ± 0.76	9.21± 0.54
4	36.56 ± 0.39	28.28 ± 0.56	21.43± 0.47
6	48.43 ± 0.26	38.08± 0.76	33.54 ± 0.43
8	62.36 ± 0.54	52.34 ± 0.21	49.36 ± 0.61
12	90.32± 0.26	68.43 ± 0.15	58.43 ± 0.43
24	-	95.32 ± 0.24	76.43 ± 0.54

Mean ± SD (n = 6)

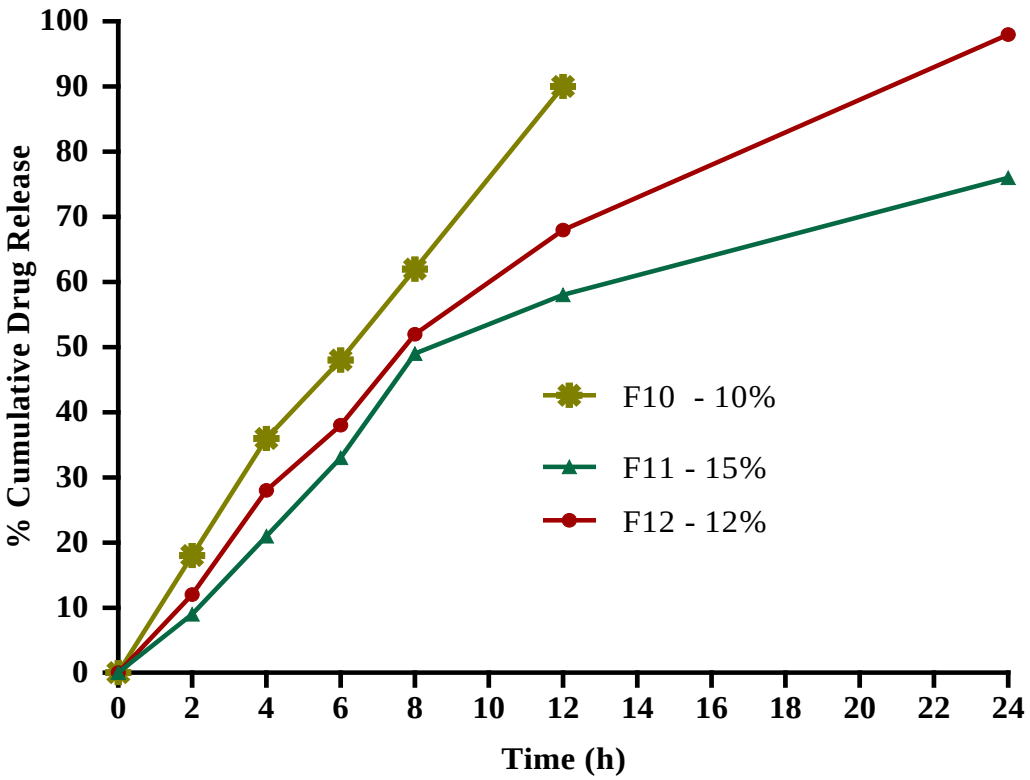

Fig.16 Effect of coating thickness on drug release

Table: 19 Effect of agitational intensity on drug release

Time (h)	% Cumulative percentage drug release		
	50 rpm	100 rpm	150 rpm
0	0	0	0
2	8.02± 0.21	10.54± 0.12	9.12 ± 0.34
4	19.21 ± 0.38	20.21± 0.43	19.21 ± 0.32
6	20.21 ± 0.19	28.43± 0.54	26.03 ± 0.21
8	28.21 ± 0.67	39.54± 0.21	36.21 ± 0.56
12	39.34± 0.54	56.21± 0.48	55.32± 0.65
24	93.21± 0.32	99.21± 0.29	98.21± 0.32

Mean ± SD (n = 6)

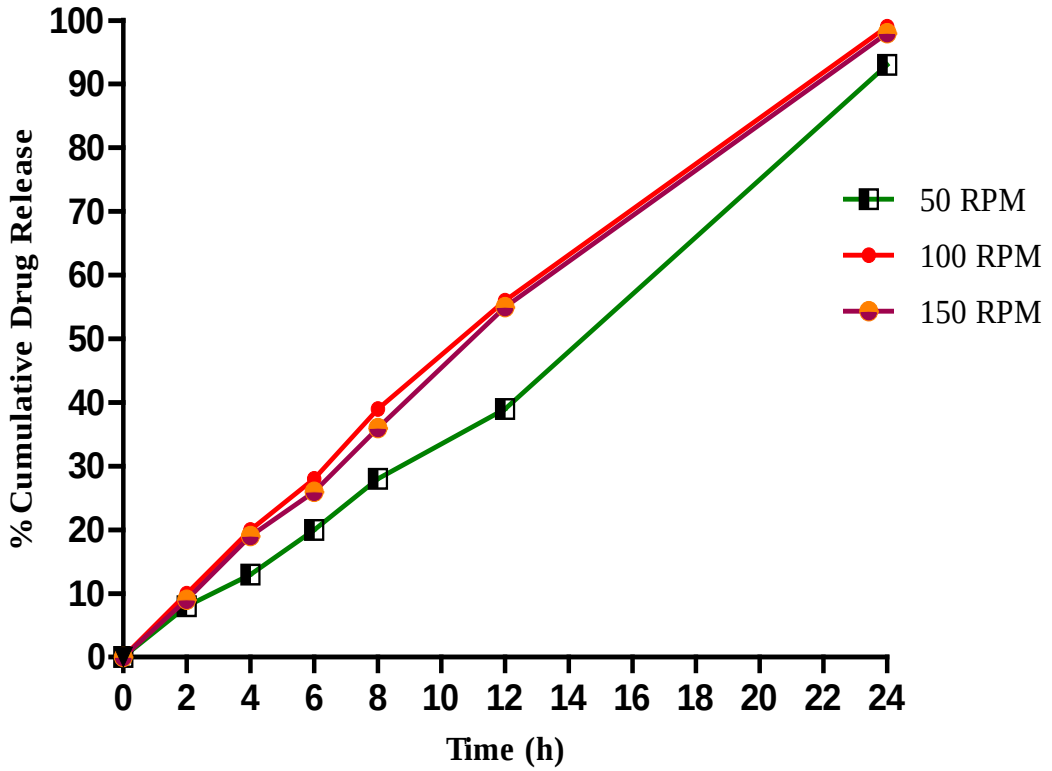

Fig.17 Effect of agitational intensity on drug release

Table: 20 Influence of pH on drug release

Time (h)	pH 1.2	pH 6.8.	pH change method
0	0.00±0.00	0.00±0.00	0.00±0.00
2	8.21 ± 0.32	10.12±0.34	12.21±0.45
4	16.00±0.00	19.43±0.00	18.45±0.12
6	22.45±0.12	29.00±0.00	26.00±0.23
8	32.43±0.12	38.43±0.34	35.12±0.44
12	45.21±0.32	55.23±0.32.	49.21±0.54
24	93.43±0.21	98.54±0.21	96.21±0.32

Mean ± SD (n = 6)

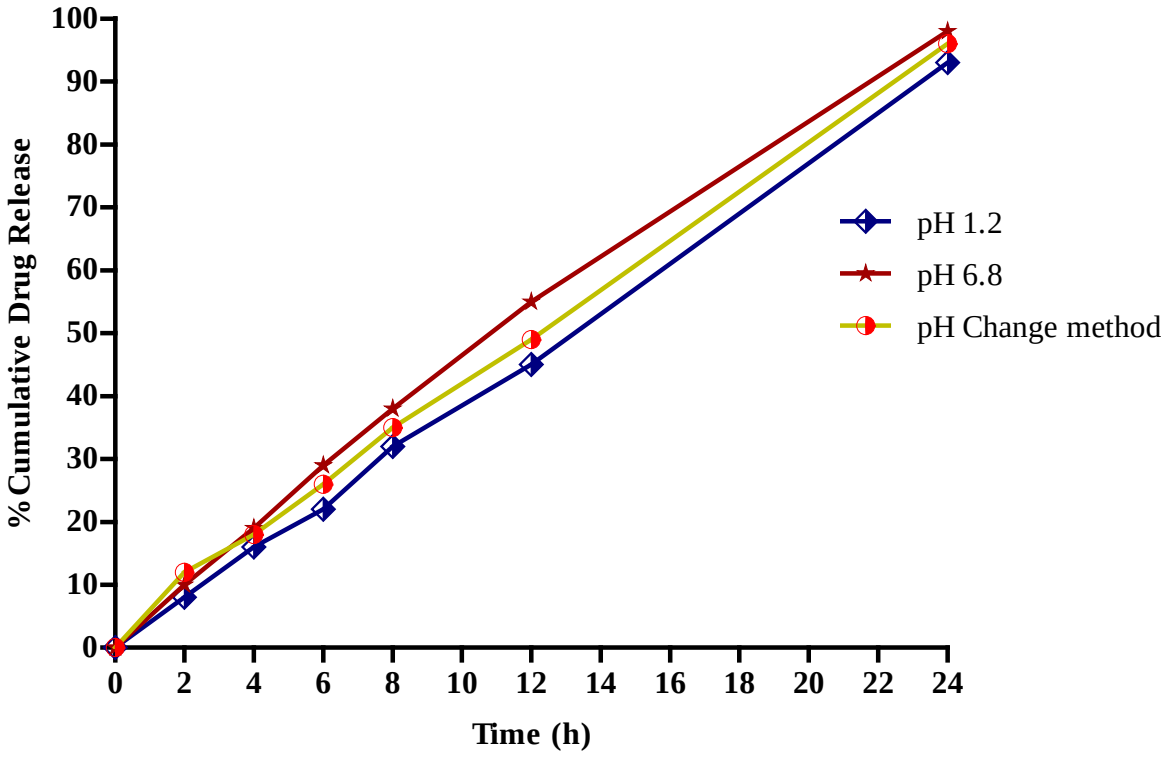

Fig.18 Effect of pH on drug release

8.4 Release Kinetics

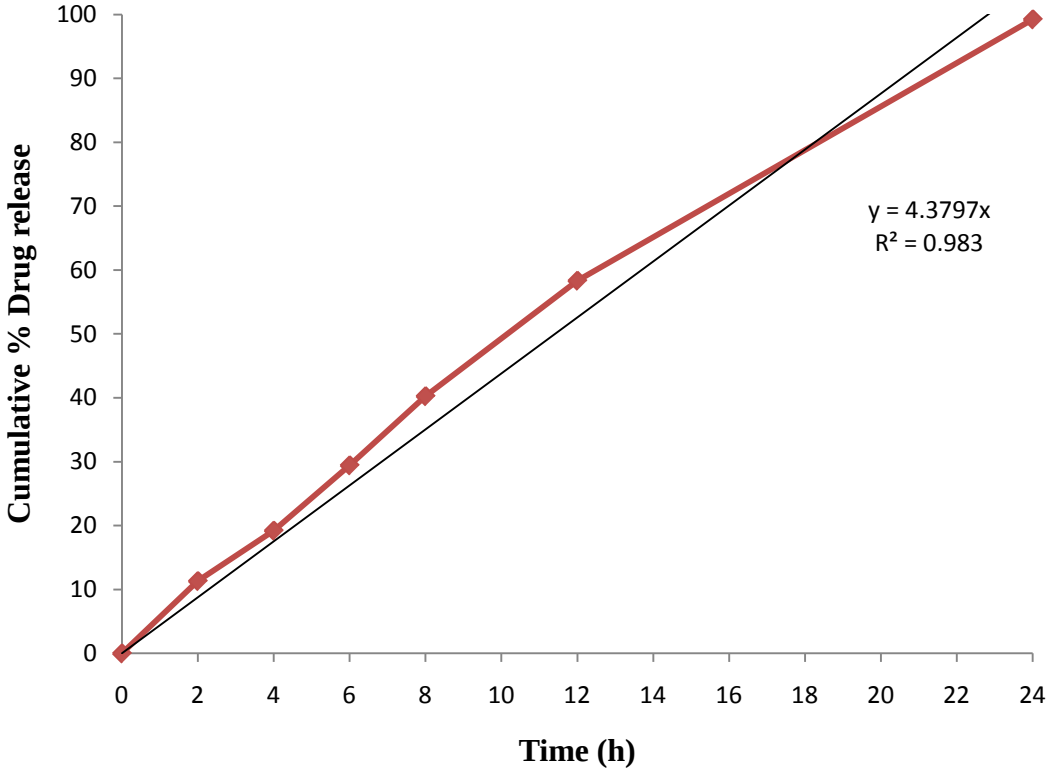

Fig. 19 Zero Order Kinetics

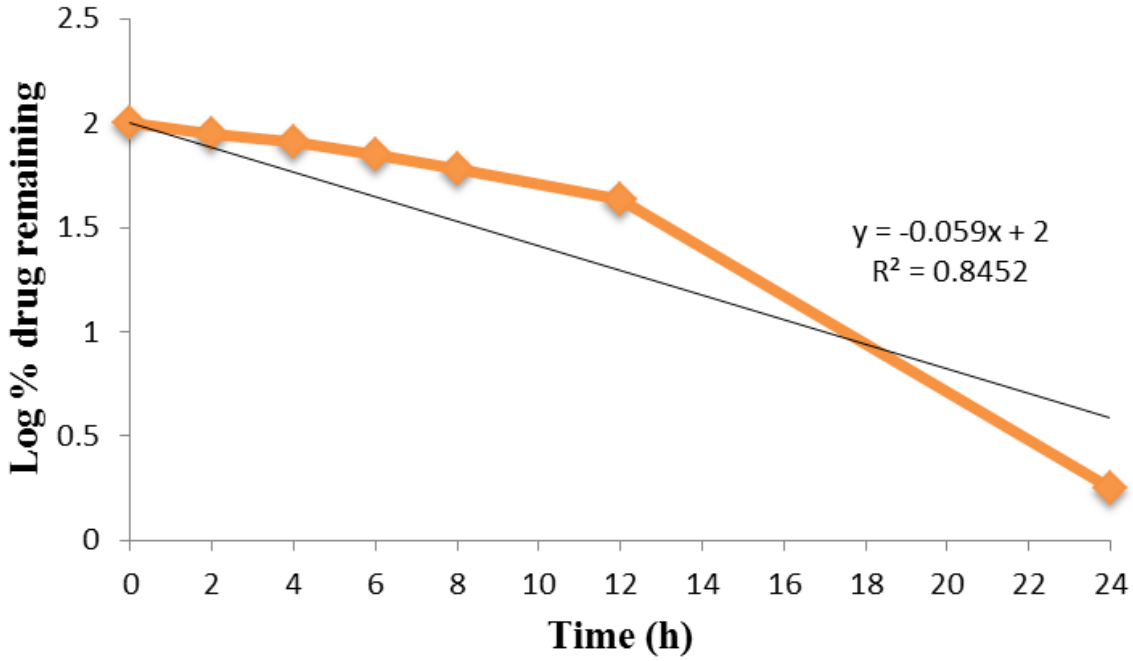

Fig. 20 First Order Kinetics

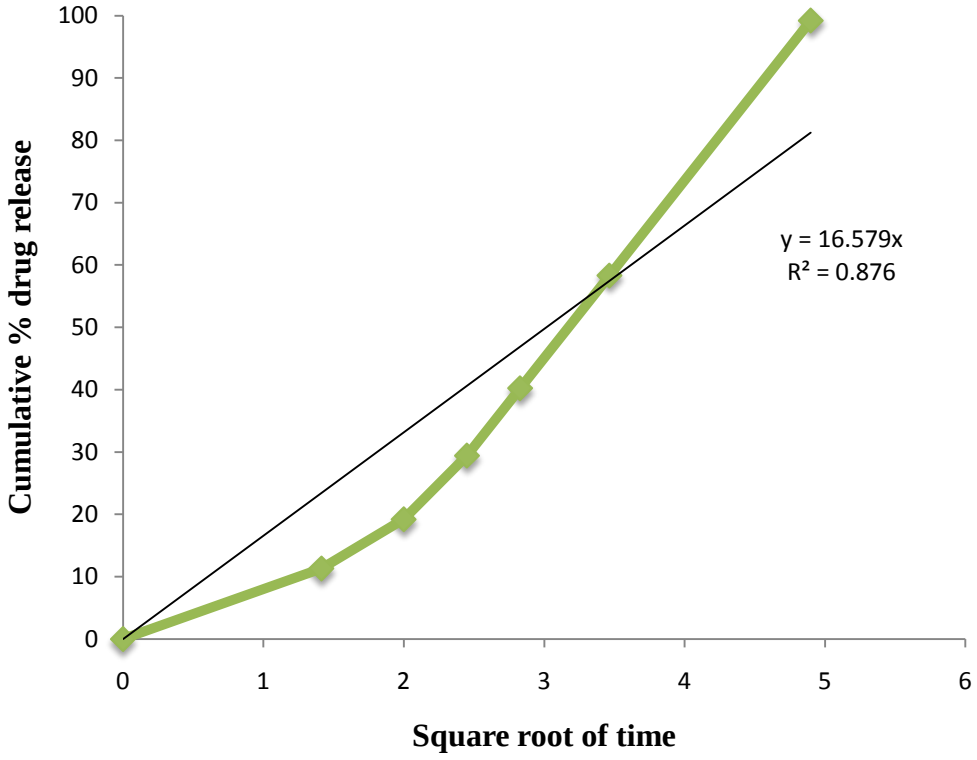

Fig.21 Higuchi Kinetics

Table: 21 Release Kinetics data to fit various mathematical models

Cumulative (%) Release Q	Time (t)	root (t)	Log (%) Release	log (t)	log (%) remain	Release Rate (Cumulative % Release/T)	1/Cum% Release	Peppas log q/100	Hixson Crowell Model	Modified Cube Root Equation
0	0	0			2				0	0
11.32	2	1.4142	1.0538	0.3010	1.9478	5.66	0.0883	-0.9461	2.2453	5.0415
19.21	4	2	1.2835	0.6026	1.9073	4.8025	0.0520	-0.7164	2.6781	7.1727
29.43	6	2.4494	1.4687	0.7781	1.8482	4.905	0.0339	-0.5312	3.0874	9.5322
40.25	8	2.8284	1.6046	0.9039	1.7763	5.03125	0.0248	-0.3952	3.4270	11.7447
58.32	12	3.4641	1.7658	1.0791	1.6199	4.86	0.0171	-0.2341	3.8779	15.0387
99.21	24	4.8989	1.9965	1.3802	-0.1027	4.13375	0.0100	-0.0034	4.6293	21.4307

Table: 22 Parameters fitted in various Mathematical Models

Parameters	R (CvT)	R(CvRoot(T))	Time vs Log©	Log T vs Log C	Rel Rate vs Cum Rel	Rel Rate Vs 1/cum Rel	Time Vs Log % Remaining
Slope	4.1250	20.7981	0.0377	0.8981	-55.208	0.0480	-0.0201
Correlation	0.9950	0.9630	0.9206	0.9980	-0.8398	0.8167	-0.9039
r^2	0.9900	0.9274	0.8475	0.9960	0.7053	0.6670	0.8171

8.5 Stability Studies

Table: 23 Accelerated Stability Study

Parameters	Storage condition 40ºC ± 2ºC & 75% ± 5%RH		
	Initial	**1st month**	**2nd month**
Average weight (mg)	490	492	489
Assay (%)	99.75	100.21	98.92

Table: 24 *In vitro* Dissolution study

Dissolution Time points	Storage condition 40ºC ± 2ºC & 75% ± 5%RH		
	Initial	**1st month**	**2nd month**
2nd Hour	12.56	11.96	12.01
4th Hour	25.12	24.97	25.08
8th Hour	42.54	42.21	41.91
12th Hour	68.21	66.32	68.32
24th Hour	98.21	97.98	98.21

9. Discussions

9.1 Preformulation Studies

9.1.1 Raw Material Analysis

From the raw material analysis of Losartan potassium it is found that all the evaluation parameters are within the specification limits given in **Table: 10.**

9.1.2 Drug-Excipient Compatibility Studies

❖ **Physical Observation**

The physical examination of all mixtures of drug and excipient has been found that no characteristic colour change and all portions of the mixture of powder are visually compatible the results were given in **Table: 11.**

❖ **FT-IR Studies**

The Infrared spectra of Losartan potassium standard drug showed sharp peaks at 3186.79, 2956.34, 2871.49, 1459.85, 1260.25, 996.053, 764.637 cm^{-1}. These peaks were found to be prominent in the spectra of physical mixture containing drug polymer and other excipients were shown in **Fig.8 and Fig.9.**

❖ **Thermal Analysis**

DSC thermograms of Losartan Potassium with Excipients depicted in the **Fig.10** showed no changes in the endotherms when compared with the thermogram of the pure Losartan Potassium in the **Fig. 11.** This was confirmed by observing the sharp melting point endotherm of Losartan potassium at 70.81ºC and coated formulation. From the DSC thermo grams it was clear that there was no specific interaction between the drug and polymer used in the present formulation.

9.1.3 Evaluation of Physical Mixture

The evaluation of physical mixture expresses that the values of compressibility index and angle of repose were found to be within the specified

limits given in **Table: 12**. From this it indicates that all the batches have good flow property and also suitable for compression.

9.3 Optimization of variables

9.3.1 Effect of Osmogent Type

From the **Table 14**, the drug release from the system may vary according to the type of the osmotic agent used. This is due to the different osmotic pressure produce by different osmotic agent. Lactose showed good and controlled release over sodium chloride upto 16 to 20 hour was depicted in the **Fig. 12**.Whereas sodium chloride, because of higher osmotic pressure the drug release was found to be completed by 12 hour. Further study has been carried out taking lactose as osmogent and also a diluent possessing little osmotic pressure (23) is given in **Table: 1**. Previously Mannitol had chosen as an osmotic in the push pull osmotic pump development[65]. Losartan Potassium being freely soluble drug it required less hydration pressure for controlled release over prolonged period of time.

9.3.2 Effect of Osmotic Agent Concentration on Drug Release

The osmotic agent was taken in both the drug layer and also in the push layer. The formulation F2, F3 and F4 containing different concentration of Osmotic agent showed different drug release given in **Table: 15**. **Fig.13** depicts the influence of osmotic agent concentration on drug release. From this F2 formulation containing 200mg of osmotic agent was optimized as it had shown drug release about 97% after 24 hours, whereas F3 showed 70% of the drug release from system after 24 hours and the formulation F4 was released much earlier than the desired release rate. F3 showed less response and the release rate is not up to the desired level. Whereas F4 shows fast release and the drug release could not be extended for 24 hours.

9.3.3 Influence of Orifice Diameter on Drug Release

Orifice diameter is one of the critical parameters that greatly affect the release rate of the osmotic drug delivery. The orifice diameter must be optimized to control the drug delivery from the osmotic system. The orifice diameter should be

reasonably large to prevent bursting of the osmotic system due to the hydrostatic pressure produced with in the system and also at the same it should not be large which results in free diffusion of the drug which in turn leads to loss of control over the release rate. **Table: 16** gives the cumulative percentage release of drug with corresponding orifice diameter. Different sizes of delivery orifice were made in the range of 250 (F7), 450 (F5), 550 (F6) and 850 µm (F2). The percentage drug released approximately from the corresponding formulations after 24 hours were 72%, 98%, 96% and the formulation F2 having higher orifice diameter showed higher release rate and hence the maximum therapeutic concentration was attained in 12 hour and the release could not be extended not more 12 hours. The formulations F5 and F6 showed release over 24 hours but among the two formulations the release of drug from the Formulation F4 showed controlled release over the F5 formulation. The comparison of release rate corresponding to orifice diameter was shown in **Fig. 14**. Orifice diameter had great influence on drug release. The formulation with 450 µm (F5) showed better response when compared with the other three formulations. The orifice diameter of 450 µm was used in further proceeding of the study.

9.3.4 Effect of Polymer Concentration on Drug Release

The release of freely soluble drugs was expected to be controlled by the Polyethylene oxide used in the lower push layer by hydrogel formation[65]. Three concentrations of Poly Ethyleneoxide of high molecular weight were taken in the lower push layer 50mg, 100mg and 200mg were taken for the study. The release rate of the drug depends upon the concentration of the polymer present in the lower layer. Fifty milligram of the polyethylene oxide taken in the lower layer causes the drug to release faster as the polymer concentration is too low. Polyethylene oxide can also be used as release retardants in case of freely soluble drug. Comparing the release rate of the formulation with different polymer concentrations 50 (F6), 100 (F7), and 200mg (F8). The Formulation (F7) containing 100mg Poly Ethyleneoxide containing formulation shows controlled release over prolonged period of time. **Table: 17** give the effect of polymer concentration on drug release and **Fig.15** represents the comparative drug release profile of three different formulations. The

formulation F6 containing 50 mg of the polymer shows release that the system had release about 90% of the drug within 12 hours, whereas the formulation F8 containing 200 mg of the polymer showed slow release rate due to its release retardant property, releases only 70 % after 24 hours. The formulation F7 containing 100mg polymer shows about 98% drug release in a controlled manner for 24 hours.

9.3.5 Effect of Membrane Thickness on Drug Release

The water influx is related to the osmotic pressure and coating membrane. Therefore the water influx is inversely proportional to coating thickness and the directly related to the osmotic pressure developed within the osmotic system. To investigate the effect of coating level on the release profiles three level of coating thicknesses were taken for the study 10 % (F10), 12 % (F12) and 15 % (F11) achieved by gaining the weight. **Table: 18** indicate the release profiles of osmotic devices formulated with different thickness. When the coating thickness increased up, the percentage drug release and release rate of Losartan potassium was observed. The increase in coating level results in the decrease of water imbibing through the membrane, thus the hydration of drug layer and expansion of the push layer were decreased resulted in decreased drug release rate. The release of drug from the formulation F10 was found to be completed by the 12^{th} hour. Whereas the drug release from the formulation F11 was found to be approximately 76% at the end of 24^{th} hour. The formulation F12 was found to have optimum release of 95% approximately compared with all the other formulations. The comparison of release profile was shown in **Fig.16.**

9.4 Evaluation of Compressed Tablets

The compressed tablet contains both the drug layer and push layer were evaluated for various physical parameters namely, Hardness, Friability, Thickness and Assay. The values obtained after evaluation was tabulated in **Table: 11,** the values indicate that the compressed tablets were having good compressibility property and the drug content values were found to be within the specified limits.

9.4.1 Influence of Agitational Intensity on Drug Release

The optimized formulation is investigated to determine the intensity of agitation on the drug release. The agitation was carried out at 50, 100 and 150 rpm. The result of agitatoinal intensity on drug release was shown in **Fig. 17**. The results showed that the drug release was not significantly affected by agitational intensity.

9.4.2 Influence of pH on Drug Release

The optimized formulation was evaluated for drug release response depending upon the physiological factors. There was no significant change in the drug release from the system in different dissolution medium. The response was shown in the **Fig. 18.**

9.6 Release Kinetics

Dissolution data of the optimized formulation was fitted to various mathematical models (zero order, first order and Higuchi) in order to describe the kinetics of drug release. Data were treated according to zero order, first order and Higuchi using least square method of analysis shown in **Table 21** and **Table 22.** Best goodness of fit test (R^2) was taken as criteria for selecting the most appropriate model. When the data were plotted according to the first order and Higuchi equations, the formulations showed a comparatively poor linearity, whereas the regression value for zero order equation indicated that the drug release from optimized formulation was independent of drug concentration.

9.7 Stability Study

The Accelerated stability of the optimized tablet had carried out for a period of two months. The optimized tablets were stored in the stability chamber at the required conditions as per International Conference on Harmonisation (ICH) guide lines. The results showed that the tablets were found to be stable and showed the same dissolution rate as in the initial stage. The stability data were given in **Table: 23 and Table: 24.**

10. Summary

Chapter I – In the introduction chapter the principle of osmosis, types of osmotic agents , classifications of oral osmotic pump, basic components of the oral osmotic pump tablets, list of patents and marketed tablets available in the markets were detailed.

Chapter II – In this chapter the literature related to this work was surveyed and a brief discussion had been given on each literature.

Chapter III – In the third chapter the scope work was discussed. The objective of the work was to develop an oral push pull osmotic pump containing an anti-hypertensive drug and to show that the developed system would follow the zero order kinetics by optimizing the various formulation variables. The formulation variables chosen for the investigation were osmogent type, osmogent concentration, orifice diameter, polymer concentration and the coating thickness.

Chapter IV - This chapter gives an idea for the proposed plan of work that has to be carried out.

Chapter V and VI - In these chapters, information about the drug and the excipients used in the study was given.

Chapter VII – This chapter deals with the materials and methods used in the present study was given. This chapter covers the details of the experimental methods including evaluation of the core tablets, optimization process, and evaluation of physical mixture and also about the release kinetics and evaluation of the osmotic pump tablet were also given.

Chapter VIII – showed the results obtained from the experimental methods were given in this chapter. In this chapter the figures and tables expressed the results graphically.

Chapter IX – This chapter provides the complete information about the results obtained and the results were analysed through various tables and graphs.

Pre-compressional parameters of the prepared tablets (bulk density, tapped density, carr's index, and angle of repose) are in the range of given in official standard, indicates that the physical mixture were found to be free flowing. The post-compressional parameters of the tablets were found to be within the limits. The optimized formulation was selected for DSC and FTIR studies did not show any interaction between the drug, polymer and excipients.

In Vitro dissolution study of formulation containing Losartan Potassium with different concentration of the osmogent (lactose) and the polymer concentration (PEO) was discussed. F 12 was found to be satisfactory, where the release of the drug was found to be approximately 12, 28, 38, 52, 68 and 95 %.

The kinetics of the drug release for formulation F 12 was calculated and plotted. The formulation F 12 follows zero order kinetics and the drug release mechanism was found to be Higuchi mechanism.

The dissolution for the optimized formulation was carried out at different agitation (50 rpm, 100 rpm, and 150 rpm). It reveals that the change in the rate of drug release due to agitation was negligible.

The dissolution for the optimized formulation was carried out at different pH (1.2, 6.8 and pH change method). It reveals that the change in the rate of drug release due to pH was negligible.

The optimized tablets F 12 were selected for stability studies were carried out according to ICH guidelines at 40º C ± 2 º C for a specific period of time indicated that the physical parameters and drug release characteristics were not altered significantly showing good stability on storage.

11. Conclusion

The Push-pull osmotic pump tablet containing 100 mg of Losartan potassium provided controlled release up to 16 – 20 hours. In this developed system, lactose used as an osmogent with the drug: Osmogent ratio of 1:2. 450 µm of the orifice diameter showed better release profile. Similarly, the drug: polymer ratio was also found to be suitable as 1:1 ratio. Finally, 12 % w/w of the thickness of the membrane was required to control the drug release up to 24 hours. The developed formulation showed no deviation in the drug release and instability of the membrane which are characterized by different pH and agitational intensity. The push pull osmotic pump of Losartan potassium was found to be stable for the 2 month accelerated stability studies. However the *invivo* - *invitro* correlation (IVIVC) needs to be done after pre-clinical evaluation.

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